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Studies on an Extra Pre-beta Lipoprotein Fraction

By G Dahlén C. Ericson C. Furberg L. Lundkvist K. Svärdsudd

Boden 1972

PAPER I

Electrophoresis of Lipoproteins on Cellulose Acetate Membrane

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Electrophoresis of lipoproteins has proved to be a convenient means of classifying lipoproteinemias and much experimental and epidemiological evidence shows that relationship exists between serum lipoprotein abnormalities and atherosclerosis. When a screening population study (II) was started in the Boden area in Northern Sweden more than a year ago we decided to carry out electrophoresis of lipoproteins as well as cholesterol and triglyceride analyses on every subject. In routine work we had sometimes observed, under fasting conditions, two distinctly separate bands in the pre-beta region also reported by some other investigators (1 4, 3 9 11) As no pathological significance had been attached to this finding we were especially interested in investigating them in an epidemiological study This decision was made in spite of the fact that blood samples for lipid analyses were taken in the afternoon instead of in the morning after overnight fasting The purpose was to get an idea of the value of lipoprotein electrophoresis in this type of epidemiological examination where preceding meal may have an effect on the lipoprotein pattern

Considering the good resolution of our electrophoretic method and the results from the population study (II) and the following studies (III—V) we found it of interest to give a full description of our method for lipoprotein electrophoresis and our principles for interpretation of changes in the pre-beta region

Methods

Blood sampling In the population study the subjects were examined in the afternoon. They were asked not to eat for 4—6 hours before the examination. The period of fasting was in most cases —3 hours longer as they had been fasting from breakfast until the examination took place at 3—5 p.m. In routine work lipoprotein electrophoresis was carried out after a 1 hours fasting period. The serum was separated by low speed centrifugation. Analyses were performed in the following morning The serum was kept at +4°C during storage. In all subjects from the population study the samples were analysed within 2 days. A storage of more than two days may influence the possibility to detect separate bands in the pre-beta region.

Reagents and equipment Veronal buffer pH 8.6 with ionic strength of 0.075 was used. All chemicals and solvents were of analytical grade. Commercially available Schiff's reagent was obtained from Merck AG Darmstadt.

Electrophoresis and quantitative scanning were carried out with the Microzone electrophoresis system (Beckman Instruments Inc, 2500 Harbor Blvd. Fullerton, Calif 926 34) including electrophoresis cells, power supply sample applicator and densitometer with scanning attachment Cellulose acetate membranes (Sepraphore III Gelman Instrument CO) were used as supporting media.

Electrophoresis procedure The membrane was soaked in fresh buffer overnight. After excess solution had been removed between blotting papers the strip was placed in the electrophoresis chamber previously filled with cooled veronal buffer exactly to the upper fluid level. Current was a

for a period of fi e minutes followed by sample application and lipoprotein separation for 1 hour and 45 min at 200 volt. The sample was applied in three consecutive applications (totally 0 75 µl) at the cathodal end and with 8 specimens on each strip

Immediately after the electrophoresis the membrane was put in a closed chamber Six to ten g anhydrous barium peroxide and 20 ml concentrated sulphuric acid respectively were then set down on opposite sides and subsequently they were mixed. After 10 min ozonation of the l pids the membrane was washed at once with 0 001 M HCl and immersed in Schiff's reagent for 2 hours After staining the membrane was washed 3 times with 0 5 % HNO and dried between blotters overn ght The membrane was mounted in a plastic envelope for storage and optical scanning Densitometry was performed at 599 nm.

Results

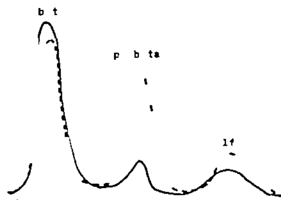
For more than a year we have used the Microzone electrophoresis system for our routine lipoprotein electrophoreses. With 2 electrophoresis cells we can easily handle more than 32 samples in one day and the whole procedure for 32 samples can be completed within 5—6 hours.

Cellulose acetate have been used as supporting material. It can be seen from Fig 1 which shows a normal pattern and a common Type IV pattern according to Fredrickson et al (6) that th s medium gives clearly separated fractions with practically no tailing

The lipophilic character of the supporting medium makes the commonly used dyes (Sudan Black B and Oil Red O) unsuitable We have therefore used the indirect staining method by Kohn (8) The fractions are strongly coloured with practically no background staining and quantitation by densitometry is eas ly obtained. The staining seems to be reasonably proportional to the quantity of the lipids in the lipoprotein fractions (Fig 2) After staining the three main fract ons alpha, pre-beta and beta can be seen in the electrophoresis.

The *alpha* lipoprotein fraction is obtained as a single band well separated from albumine which in some cases can be seen as a slight discoloration.

Except for a well separated *pre bet* band adjacent subfractions might in some cases be observed In samples from some subjects a slow migrat ng



F g 1 Normal lectrophoretic pattern (——) nd Type IV pa ern ( ) according to Fredrickson



F g Relat on of triglyceride lues to the relati peak rea of the pre beta l poproteins

fraction appears (Fig 3 cases 4 and 6) and in the screening population study previously mentioned this fraction was found to be correlated with symptoms of angina pectoris (4 5 7 II) We have called this fraction the pre-beta 1 fraction. Fig. 4 shows lipoprotein patterns with pre-beta 1 of different sizes. In a few cases the region between the pre-beta and beta fractions was covered and a distinctly separated fraction could not be discovered. Due to the good separation and the almost normal distribution of the fractions it is however reasonable to believe that in these cases as well, a hidden fraction is present.

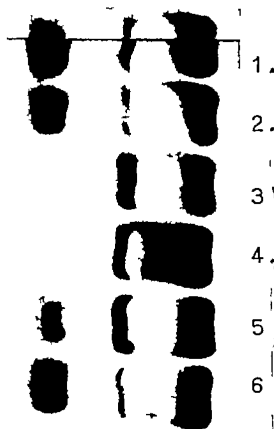


Fig 3 A stained membrane showing electrophoretic patterns from 6 subjects. Cases 1 and 2 have normal electrophoretic pattern. Cases 3 4 and 5 have high triglyceride values, case 5 also has high cholesterol value A pre beta 1 fraction is clearly seen in cases 4 and 6

Close to the pre-beta fraction an indication of small unresolved fractions like those exemplified in Fig. 5 was sometimes obtained. As they could not be verified by ocular inspection of the membrane they have not been classified as pre beta 1 fractions.

We have been able to verify the pre-beta 1 fraction by lipoprotein electrophoresis in 0 5 % agarose and lipid staining with Sudan Black B The separation between pre-beta-1 and pre-beta was however not quite as good with that method (10)

The *beta* band is sometimes split into two fractions. Repeated blood samplings after a test meal show that variations occur in these fractions as well as in the pre-beta fractions (IV)

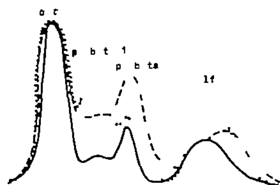


Fig. 4. Electrophoretic patterns showing pre-beta-1 fraction of differing size

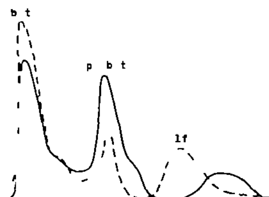


Fig 5 Electrophoretic patterns showing small subfractions close to the pre-beta fraction

Chylomicrons if present remain at the point of sample application.

Table I shows the calculated values for each fraction from 8 different applications of the same serum sample with a pre-beta 1 fraction. In Table II reference limits, standard deviations and coefficients of variation for the beta, pre-beta and alpha bands are given for 22 blood donors. In routine work pre-beta-1 and a second beta fraction are not calculated separately but included in the total pre beta and beta values respectively. The lipoprotein patterns of fasting patients then conform well to the Fredrickson classification of hyperlipaemia.

TABLE I. Relative peak areas for the beta pre beta-1 pre beta and alpha fractions respectively in eight applications from the same subject

BETA %	PRE BETA 1 %	PRE BETA %	ALPHA %
53	11	31	6
54	11	30	5
51	11	29	9
52	10	30	7
53	9	30	7
50	10	35	5
53	8	33	6
49	12	31	8

TABLE II. Standard deviations and coefficients of variation calculated from 22 blood donors and our present reference limits

	BETA	PRE BETA	ALPHA
Standard deviation	± 3.5	± 1.8	± 1.7
Coefficient of variation (%)	6.1	9.1	6.4
Reference limits (m ± 3 SD) (%)	43—64	14—26	21—32

Discussion

Our method for electrophoresis of lipoproteins with Sepraphore III membranes as supporting medium has good resolution and good reproducibility. It is also a simple and convenient routine method. The separation is good enough to reveal several pre-beta bands that may be of clinical importance.

We have often found a pre-beta 1 fraction in normolipidemic subjects and this may indicate that electrophoresis of lipoproteins can be of value even in subjects with normal cholesterol and triglyceride values. Investigations of the chemical composition and the immunological characteristics of the different pre-beta bands are in progress.

The correlation between pre-beta 1 and clinical findings presented in the following papers (II III IV and V) shows that it might be important to perform electrophoresis of lipoproteins in addition to cholesterol and triglyceride analyses in health screening investigations. We consider our method suitable for this purpose as well as for routine work.

Summary

A simple and convenient method for electrophoresis of lipoproteins on Sepraphore III membranes is described. The reproducibility and resolution are good. Several bands are often revealed in the pre beta region. A description of our interpretation of the electrophoretic pattern is given.

References

1 BEAUMONT J L, CARLSON L A COOPER, G R, FEJFAR, Z, FREDRICKSON, D S & STRASSER, T Classification of Hyperlipidaemias and Hyperlipoproteinaemias Bull. Wld Hlth Org 43 891 1970.

2 BECKERING Jr R E & ELLEFSON, R D A Rapid Method for Lipoprotein Electrophoresis Using Cellulose Acetate as Support Medium. Am. J Clin Path 53 84, 1970

3 CORNELISSEN, P J H C & ROELOFS-FIZAAN, L E A M Electrophoretic Separation of Lipoproteins Clin Chim Acta 29 344, 1970

4 DAHLÉN, G ERICSON, C, FURBERG C LUNDKVIST L & SVÄRDSUDD K Lipoprotein pattern in IHD In Towards Preventi Cardiology Eds KEYS, A & TIBBLIN G Almqvist & Wiksell, Uppsala (In print)

5 DAHLÉN, G & ERICSON C A New Lipoprotein Pattern in Patients with Angina Pectoris Scand. J Clin Lab Invest Suppl 118 54, 1971

6 FREDRICKSON D S LEVY R I & LEES, R S Fat Transport in Lipoproteins — An Integrated Approach to Mechanisms and Disorders. New Engl J Med. 273 34, 94, 148, 215 273, 1967

7 FURBERG C, DAHLÉN G ERICSON, C, LUNDKVIST L & SVÄRDSUDD K Lipoproteiner och koronarsjukdom. Communication at Sv Läkaresällsk. förhandl Stockholm 1971

8 KOHN L A Lipoprotein Staining Method for Zone Electrophoresis. Nature 189 312, 1961

9 NOBLE, R P HATCH, F T MAZRIMAS, J A LINDGREN F T JENSEN, L C & ADAMSON, G L Comparison of Lipoprotein Analysis by Agarose Gel and Paper Electrophoresis with Analytical Ultracentrifugation. Lipids 4 55, 1969

10 PAPADOPOULOS, N M & KINTZIOS L A. Determination of Human Lipoprotein Patterns by Agarose Gel Electrophoresis. Anal Biochem. 30 421 1969

11 WILLE, L E A Slow Moving Prebeta lipoprotein Band in Serum Acta med scand 188, 241 1970

PAPER II

Angina of Effort and an Extra Pre-beta Lipoprotein Fraction

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In 1970 a screening population study among men born in 1910—1929 was started in an area around the town of Boden in Northern Sweden. The aim of this multifactor study was to identify subjects with high risks of ischemic heart disease and to modify the risk factors. Cholesterol and triglycerides are well established risk factors for the development of myocardial infarction. In the examination serum lipid analyses (cholesterol and triglycerides) were carried out.

In connexion with the population study it was considered of interest to include lipoprotein electrophoresis with the lipid analyses to evaluate its value in this type of population study.

There have been reports in recent years about the appearance of several pre-beta bands in the electrophoresis of lipoproteins (1, 2, 3, 6, 8). No pathological significance has yet been ascribed to these (1).

Material

The subjects in this report are men from a screening population study born in 1910—1914 and living around Boden. Every second man in the region (n = 396) was invited to take part in this population study. Eighty-one per cent (n = 321) answered a questionnaire and came for medical examination. Most of them were healthy and fully employed.

In total the study group was 286 men between the ages of 56 and 60 years. The electrophoretic examinations in 39 subjects have been excluded mainly because it was not possible to interpret the electrophoresis. Thirty men of those had hyperlipemia with a broad pre-beta band that made it impossible to decide whether or not an extra pre-beta band was present.

Methods

A postal questionnaire dealing with smoking habits, physical activity, stress and cardiovascular disease (family history and symptoms) was sent to the subjects before the medical examination. An abbreviated version of the London School of Hygiene Cardiovascular Questionnaire was used to identify subjects with angina pectoris of effort. In addition all men had to answer if they got precordial pain when doing heavy work with their arms, when working on cold winter days or when they became upset. All the men that answered yes to the questions about precordial pain were interviewed by us to get a clinical diagnosis of the symptoms. The WHO criteria for angina pectoris of effort (AP) were used (7). Patients who within the last two years had experienced such symptoms occasionally when doing heavier work than normal during the winter season have been regarded as cases with suspected angina of effort. Prompt relief of the chest symptoms when they stopped or slowed down has also been required for that diagnosis.

Blood sampling. The subjects were examined in the afternoon. They were asked not to eat within 4 to 6 hours before the examination. The period of fasting has in most cases been another 2—3 hours as they had been fasting from breakfast until the time when the examination took part at about 3 to 5 p. m.

Electrophoresis and quantitative scanning were performed with a Beckman Microzone electrophoretic system including electrophoresis cells, power supply, sample applicator and densitometer with scanning attachment. Cellulosa polyacetate Gelman Sepraphore III was used as the supporting medium. A description of the electrophoretic

procedure used for the separation of the lipoproteins, including handling of lipids, running technique and staining, was gi en in the previous paper (1) The interpretation of the electrophoresis was made by two of us (GD and CE) independent of each other The occurrence of a pre-beta 1 fraction was accepted only if both agreed. No information was given to them about the subjects and their diagnosis.

Determinations f trigl) erides (4) and choles terol (5) were performed with autoanalyser technique Triglyceride alues ≥2,- mmol/l and cholesterol alues ≥3?0 mg% were considered as abnormal under *fasting conditions in our routine* work. The same limit was used for cholesterol in the population study For the triglycerides we ha e used a higher limit in the population study ≥-9 mmol/l, due to the shorter period of fasting

ECGs at rest were recorded with standard leads I II III and un polar extremity leads aVR, aVL and aVF *in all men taking part in the population* study Some patients who were called for a second examination carried out a standardized work test on a bicycle ergometer

Chi²-test was used for testing the signif cance of differences

Results

Lip d analyses

According to criteria given above 1 men had elevated cholesterol values only and 58 men elevated triglycerides only 10 had both cholesterol and triglyceride values elevated.

Electrophoresis of lipoproteins

An extra electrophoretic fraction between the beta and pre-beta band, named pre-beta 1 (Fig. 1) was found in 37 men (?0%) This subfraction aried n size (cf I) No pre-beta 1 fraction was found in the rest of the men from the population study (Fig 2)

In the presence of a broad pre-beta band it was difficult to determine the occurrence of a pre beta-1 fraction Fig. 3 shows the electrophoretic pattern in one patient before and after diet therapy It seems possible that the broad pre-beta band recorded on the first occasion was covering the pre-beta-1 fraction

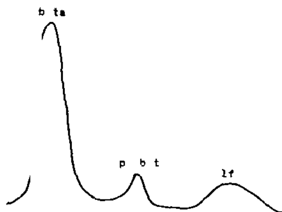


Fig A normal electrophoretic pattern

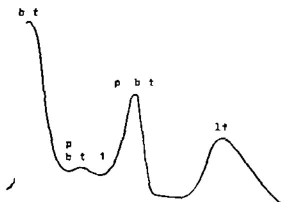


Fig. 1 Electrophoretic pattern show g pre-beta 1 fraction

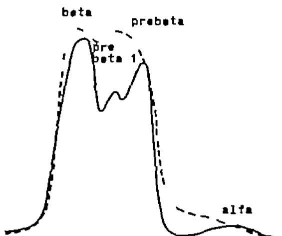


Fig 3 Electrophoretic pattern before ( ) and after (———) diet therapy

Prevalence of angina pectoris of effort

Chest symptoms typical of angina pectoris (AP) according to clinical judgement was found in 32 men (11%) Out of these men, 5 had a history of a myocardial infarction. In addition 21 men were judged as cases with symptoms suspected for AP 11 more men had atypical chest pain i e. they had precordial pain according to the questionnaire but no history of typical or suspected AP or other diagnoses such as rhizopathia, bronchitis or other chest diseases

Pre-beta-1 and precordial pain according to questionnaire

Precordial pain or discomfort when walking uphill or in a hurry according to questionnaire was found in 68 men Out of these 21 had a pre beta 1 fraction as opposed to 47 lacking this extra fraction (Table I) The percentage of men with pre-beta 1 was 31 in the group with precordial pain according to the questionnaire and 17 in the group with no chest pain. This difference between the groups is statistically almost significant ($p<0\,05$)

Among the men with pre-beta 1 fraction 28 men (31%) answered in the questionnaire that they got precordial pain when doing heavy work with their arms, when working on cold winter days and/or when they became upset. Most of these men also got precordial pain when they walked uphill or hurried. Among the men with no such chest pain 29 (15%) had pre-beta 1 fraction. The difference between the groups is statistically significant ($p<0\,01$) (Table I)

Pre-beta-1 and angina pectoris of effort according to the clinical examination

In the group of men with the pre-beta-1 fraction 24 men (45%) were diagnosed as cases with typical or suspected AP on the other hand 33 men (14%) with no AP had a detectable pre-beta-1 fraction The difference between the two groups is highly significant ($p<0\,001$) (Table I)

If also men with atypical chest symptoms were included with those with typical and suspected AP the following distribution was found in men with pre beta 1 fraction 30 (46%) had one of these diagnoses, as compared to 27 (12%) with no AP

TABLE I The correlation between pre-beta 1 fraction in the electrophoresis of lipoproteins and chest pain according to the questionnaire and angina of effort according to clinical examination respectively in 286 men 56 to 60 years old

n=286	Pre-beta-1 (n=57)	No pre-beta 1 (n=229)	Difference
Questionnaire			
Chest pain when walking uphill or hurrying (n=68)	31% (n=21)	69% (n=47)	$Chi^2=5{,}83$
No such chest pain	17% (n=36)	83% (n=182)	$p<0{,}02$
Chest pain when doing heavy work with the arms, when working on cold winter days and/or when being upset (n=89)	31% (n=28)	69% (n=61)	$Chi^2=9\,74$
No such chest pain	15% (n=29)	85% (n=168)	$p<0{,}01$
Clinical examination			
Typical or suspected AP (n=53)	45% (n=24)	55% (n=29)	$Chi^2=24{,}3$
No AP	14% (n=33)	86% (n=200)	$p<0{,}001$
Typical or suspected AP and atypical chest pain (n=64)	46% (n=30)	54% (n=34)	$Chi^2=35\,4$
No AP or atypical chest pain	12% (n=27)	88% (n=195)	$p<0{,}001$

PAPER III

Familial Occurrence of an Extra Pre-beta Lipoprotein Fraction

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In a screening population study in the Boden area in Northern Sweden we have found an extra pre-beta lipoprotei in about 0 per cent of 286 men between the ages of 56 and 60 years The occurrence of this extra fraction called pre-beta 1 bore a strong correlation to symptoms of schemic heart disease (II) Among these men who had a pre beta 1 fraction there were two pairs of brothers. It was considered of interest to examine thei famil es to get an idea of whether there was a genetic factor volved in the appearence of th s electrophoretic pattern.

Material

Family 1 consists of 9 brothers and sisters of the second generation their wives/husbands and their children of the third generation. The subjects of the second generation were between the ages of 41 and 60 years and thei examined children were between 11 and 32 years of age Subject no 8 of the second generation and subjects o 3 and 15 of the th rd generation have not been examined.

Family 2 consists of 7 brothers and sisters of the second generation thei wi es/husband and their children of the thi d generation The ages of subjects f the second generation were between 46 and 62 years and their examined children were between 15 and 30 years of age Subjects no 1 3 and 6 of the second generation and subjects no 5 and 1 of the youngest generation have not been examined

Methods

Electrophoresis of lipoproteins was performed according to method previously described (I) Cholesterol and triglyceride values were determined with autoanalyser technique (II)

The members of Family 1 were examined in the same way as the men of the population study (II) They were asked to come for a blood sample to be taken in the afternoon 4 to 6 hours after a meal

The members of Family 2 were examined under more standardized conditions. The first blood sample was taken in the morning after overnight fasting and the second 8 hours after a test meal described in the paper IV

Results

Cholesterol and triglyceride values

Family 1 Subject no 9 of the second generation had high cholesterol and very high non-fasting triglyceride values. Subjects no 2 and no 3 had high triglyceride values but normal cholesterol values. The rest of the subjects of both generations had serum lipids below our upper limits (Table I)

Family 2 All the subjects examined had normal cholesterol and triglyceride values after overnight fasting except for subjects no 2 and no 3 of the second generation who had high triglyceride values (Table I)

TABLE 1 Age, cholesterol and triglyceride values in the examined subjects of the second and third generations of Family 1 and Family 2.

Generation	FAMILY 1 Subject No	Age yrs	Cholesterol mg%	Triglycerides mmol/l	FAMILY 2 Subject No	Age yrs	Cholesterol mg%	Triglycerides mmol/l
II	1	60	177	2,4	1	—	—	—
	2	57	196	3,0	2	60	241	4,4
	3	56	239	3,3	3	—	—	—
	4	50	132	2,6	4	57	242	1,2
	5	47	209	2,8	5	55	191	3,4
	6	45	229	1,1	6	—	—	—
	7	44	232	1,7	7	46	244	1,2
	8	—	—	—				
	9	40	450	12,6				
III	1	32	191	2,5	1	30	221	1,3
	2	27	186	0,3	2	[illegible]	207	1,3
	3	—	—	—	3	27	175	1,1
	4	25	172	1	4	[illegible]	182	1,0
	5	1	132	1,2	5	—	—	—
	6	30	220	1,1	6	30	189	1,0
	7	28	218	1,5	7	28	249	1,2
	8	23	194	1,1	8	25	175	0,8
	9	17	130	1,9	9	23	195	1,1
	10	23	243	1,3	10	18	154	1,0
	11	17	161	0,8	11	15	222	1,3
	12	18	141	1,0	12	—	—	—
	13	15	205	1,6				
	14	11	180	0,7				

Electrophoresis of lipoproteins

Family 1 The pedigree of Family 1 (Fig. 1) shows that 6 out of 8 relatives of the second generation had a pre-beta 1 fraction in the electrophoresis. The same extra fraction was found in the wife of one of the brothers and in two of her children. The rest of the subjects from this family had no detectable pre-beta-1 fraction.

Family 2 The pedigree of Family (Fig.) shows that 3 out of 4 examined subjects of the second generation and 6 out of 10 examined children had a pre-beta 1 fraction on their first and/or second electrophoresis. The rest of the subjects of the two generations had no detectable pre-beta 1 fraction on either of the two examinations.

Presence of ischemic heart disease

Family 1 The eldest brothers no 1 and no 3 of the second generation had a history of angina pectoris of effort. Brother no 2 was admitted to the hospital with an acute myocardial infarction during the final preparation of this paper. The youngest brother has for some years been receiving treatment for atrial fibrillation. The wife with the extra pre-beta band had an AV-block of the first degree at the ECG recording. The remaining subjects of this family had no symptoms of ischemic heart disease.

Family 2 The eldest brother examined of the second generation has a history of two myocardial infarctions. His father died suddenly in the street at the age of 60 years probably from a heart attack. The rest of the examined subjects from this family had no symptoms of ischemic heart disease.

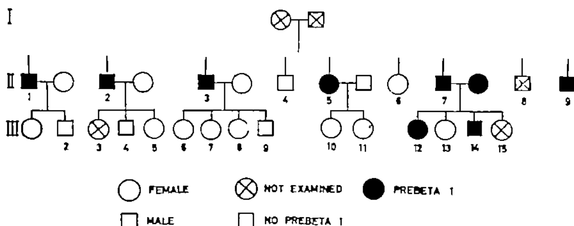


Fig. 1 Pedigree of Family 1 with the pre-beta 1 fraction in the electrophoresis of lipoproteins.

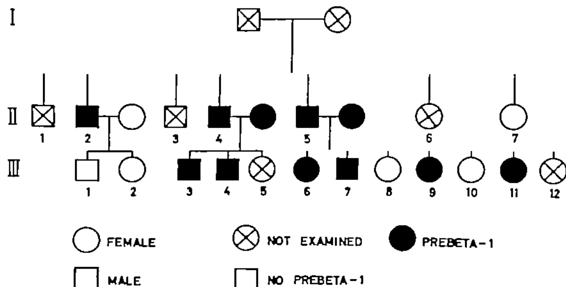


Fig. 2 Pedigree of Family 2 with the pre-beta-1 fraction in the electrophoresis of lipoproteins

Discussion

The results from this study indicate that the occurrence of pre beta 1 is genetically determined. The mode of inheritance is not quite clear from the pedigree of Family 1. The observations are consistent with both polygenic inheritance and autosomal dominant inheritance with reduced penetrance.

It is, however possible that the number of subjects with a pre-beta 1 might have been higher if the subjects had been examined under standardized conditions (cf IV). The trait studied would, in that case, also have been changed.

Family 2 was examined on two occasions, in the morning after overnight fasting and 8 hours after a test meal. Judging from the pedigree of Family

2 it seems that there is an autosomal dominant inheritance. Some further families need to be studied before the mode of inheritance is made quite clear. These studies should preferably be done in connexion with a test meal.

Different types of familial hyperlipoproteinemia have been recognized since Fredrickson established the classification of hyperlipoproteinemia. Familial Type II A and Type IV hyperlipoproteinemia are both characterized by accelerated atherosclerosis especially in the coronary arteries. Basic information of these familial disorders have been presented by Fredrickson & Lees (1) and Sanbar (2)

The correlation between the occurrence of a pre-beta 1 fraction and ischemic heart disease has been commented on in papers II and V. In paper V it is proposed that the pre-beta-1 fraction is involved in the development of ischemic heart disease. This proposition is to some extent supported in the present study by the fact that symptoms of ischemic heart disease were present in the three eldest brothers of Family 1 and the eldest subject examined of Family 2. All of them had a pre beta 1 fraction. They were all 56 years old or older at the time of the examination and their chest symptoms had occurred during the last few years. The future will show if the younger subjects of the second and third generations in both families with a pre-beta-1 fraction will develop symptoms of ischemic heart disease.

Summary

A genetic study of two families from the Boden area is presented. It appears that the occurrence of a pre-beta 1 fraction is genetically determined. The mode of inheritance is not quite clear but it may be an autosomal dominant inheritance. Further studies are required and they should preferably be done in connexion with a test meal. An interesting observation in this study is that the three eldest subjects in the first family and the eldest one in the second family had developed symptoms of ischemic heart disease during the last few years. All these subjects had a pre-beta-1 fraction.

References

1 FREDRICKSON D S & LEES, R S Familial Hyperlipoproteinemia In The Metabolic Basis of Inherited Diseases Eds STANBURY J B WYNGAARDEN J B & FREDRICKSON D S Mc Graw Hill, New York 1966

2 SANBAR, S. S. Hyperlipidemia and Hyperlipoproteinemia Little, Brown and Co. Boston 1969

PAPER IV

Variations in Pre-beta Lipoproteins after a Test Meal

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In the population study (II) a highly sign ficant correlation was shown to exist between the occurrence of an extra pre-beta fraction in the electrophoresis and symptoms of angina of ffort in men of 56 to 60 years living n Northern Sweden. During tests conducted to reproduc this electrophoretic pattern t was noted that this extra fraction named pre-beta 1 was not always detec table after overnight fasting

The subjects in the related population study were asked not to eat for 4—6 hours before the examination. All of them were nterviewed about the fasting period before the blood sampling. Most of the subjects had been fasting from breakfast until the examination that took place at about 3 to 5 p.m This means a fasting period of about 6—8 hours for most subjects

Preliminary d etary studies have shown that the extra pre-beta fraction appears after meals containing fat. A certai test meal was composed in an attempt to standardize the cond tions for this study It was considered of nterest to study the ariations of the pre-beta 1 fraction after such a standard zed breakfast

Material

The pat ents in this study were selected from among the 786 men who took part in the population study reported n paper II and from some healthy control subjects from the laboratory staff in order to elucidate d fferent patterns. About 25 men ha e been reexamined with serum lipid analyses at arious intervals after test meal This group consisted f some subjects w th a detectable pre-beta 1 fraction and others with a normal electrophoretic pattern. Out of this group 5 subjects were chosen as cases with different electrophoretic patterns after the test meal

Subject GM is 59 years old building-worker with a typical angina of effort and normal serum l pids.

Subject FS is a man 60 years old with angina of effort and high serum lipids.

Subject EL is 58 years of age and has a history of myocardial infarction.

Subject SE is a man 60 years old who is appa rently healthy and has normal serum lipids

Subject JE s a healthy man aged 30 who is working at the laboratory

Methods

Electrophor s of lipoproteins was performed according to a method described in previous paper (I)

Proced re The subjects came to the laboratory in the morning after overnight fasting. A blood sample was taken Afterwards a breakfast was given them consisting of 2 eggs, 2 dl of ordinary milk and 2 slices of white bread with butter The total calorie content has been estimated at about 600 Cal and the fat content at about 31% Blood samples were taken 1 3 5 7 9 and 11 hours respecti ely after the meal. The subjects were allowed to drink water and smoke dur g the day

Results

The electrophoretic patterns in fasting and after the test meal from subject GM with typical angina of effort are shown in Fig. 1 No extra fraction was detectable in the fasting sample. Five hours after the test meal it appears that the ordinary pre beta band had split into two fractions. These fractions were seen more clearly separated 7 hours after the meal. Two hours later there were still two pre-beta fractions. Eleven hours after the meal there was only one fraction in the pre-beta region similar to that in the overnight fasting sample.

The corresponding patterns from subject FS are shown in Fig. 2. This man had a typical angina of effort and high serum lipids. After overnight fasting he had only one pre-beta band. The pre beta 1 fraction in this case was not detectable until 9 hours after the meal. It was still present 11 hours after the breakfast. In this case another subfraction on the alpha side of the ordinary pre-beta band was seen 3 hours after the test meal This fraction could be seen, even 11 hours after the test meal. Subjects with such extra fractions on the alpha side of pre-beta have not been included in the pre-beta 1 group

It sometimes occurred that a pre-beta-1 fraction was present in blood samples taken after overnight fasting as in subject EL (Fig. 3) A pre-beta-1 fraction was seen or suspected in all electrophoreses during the day A faint fraction could be seen in the fasting sample and 1 hour after the meal. Three hours after the meal it was not clearly separated but reappeared 5 hours after the meal. The pre-beta-1 fraction was most clearly seen 9 hours after the test meal.

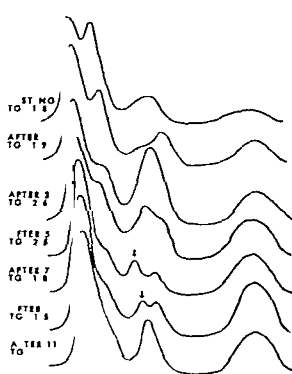


Fig. 1 Electrophoretic patterns and triglyceride values after overnight fasting and 1 3 5 9 and 11 hours respectively after test meal from normolipemic man (GM) with angina of effort

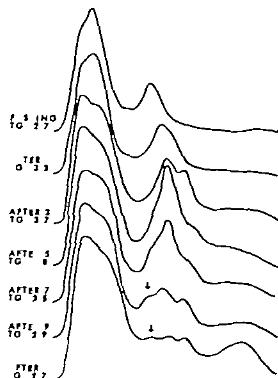


Fig. 2 Electrophoretic patterns and triglyceride values after overnight fasting and 1 3 5 7 9 and 11 hours respectively after test meal from hyperlipemic man (FS) with angina of effort.

In Fig. 4 the electrophoretic patterns after the test meal from a healthy middle aged man (subject SE) with normal serum lipids are shown. No pre-beta 1 fraction was detectable after overnight fasting. One to five hours after the meal a small subfraction on the alpha side of the pre-beta band similar to that recorded in subject FS could be seen. Only one ordinary pre-beta band was seen between 7 and 11 hours after the test meal.

Subject JE had a normal electrophoresis with an ordinary pre-beta band after overnight fasting as well as on all occasions after the test meal (Fig. 5).

There were also other minor changes in the electrophoretic pattern seen during these serial examinations. This was particularly true of the beta region which can be seen in Figs. 1, 2 and 5.

Discussion

The occurrence of a pre-beta 1 fraction in our population study (II) was high, about 20 per cent. This figure is much higher than those given in most previous reports (cf. I). Bergström (1) however found in a group of medical students a doubled pre-beta band in about 20 per cent. These discrepancies may be due to differences in methods and particularly to the duration of the fasting period before blood sampling. In the present study we have observed that several subjects with an ordinary electrophoretic pattern in the fasting state got a pre-beta-1 fraction 5 to 9 hours after a meal. It sometimes occurred that the extra fraction had disappeared 11 hours after the meal. Fasting samples in the morning are often taken about 12 hours after the evening meal the day before.

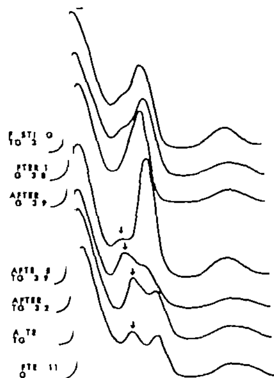


Fig. 3. Electrophoretic patterns and triglyceride values after overnight fasting and 1, 3, 5, 7, 9 and 11 hours respectively after test meal from man (EL) with history of myocardial infarction.

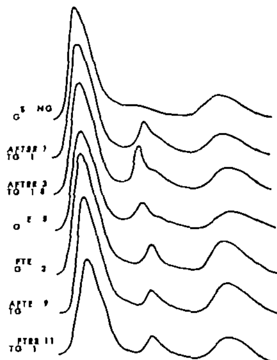


Fig. 4. Electrophoretic patterns and triglyceride values after overnight fasting and 1, 3, 5, 7, 9 and 11 hours respectively after test meal from healthy middle-aged man (SE).

It was observed that the pre-beta 1 fraction appeared later after a test meal in patients with high serum lipids than in normolipemic subjects (Figs 2 and 3) This means that there might be a number of "false negative electrophoreses in hyperlipemic subjects in our population study as samples for lipid analyses were usually taken 6—8 hours after their breakfast. In the presence of a broad pre-beta band it was also more difficult to detect an extra pre-beta band (II) Thus suggests that the total number of subjects with pre beta 1 among those with high serum lipids is underestimated in our population study To get a more accurate estimation of the occurrence of a pre beta 1 in groups of patients with high serum lipids the examination in connection with a test meal should include one sample taken after overnight fasting (about 12 hours after the evening meal) and a second sample 8 hours after the test meal This method was used in the next study (V) where patients with a history of myocardial infarction were examined.

Test meals of other compositions have also been given to men with a pre-beta 1 fraction emerging on the electrophoresis after the above-mentioned test meal These studies have shown that no extra fraction occurs within 8 hours of a glucose load (150 g sugar) (To be published)

The nature of the pre-beta 1 fraction is not established. The result of this study and some preliminary unpublished data lead us to believe that the extra fraction is a pre-beta lipoprotein per se. Judging from Fig 1 it seems that pre-beta-1 emerges from the ordinary pre-beta band and that the extra fraction in some way reflects a change in the composition of the ordinary pre-beta band. Some chemical studies of the pre-beta 1 fraction are currently being made but nothing can as yet be concluded from them.

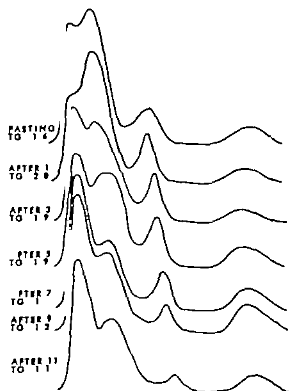


Fig. 5 Electrophoretic patterns and triglyceride values after overnight fasting and 1 3 5 7 9 and 11 hours respectively after test meal from healthy young man (JE)

Summary

Variations in the pre-beta lipoproteins have been studied after a test meal (standardized breakfast) in a group of men. It is concluded from this study that the pre-beta-1 fraction may not appear until about 6—8 hours after a test meal and that it has often disappeared 11 hours after the meal This probably explains why pre-beta 1 is not regularly detectable in routine electrophoresis performed in the morning after overnight fasting. The pre-beta 1 fraction is frequently occurring later in subjects with high serum lipids than in normolipemic subjects. It is assumed that pre beta-1 is induced by food and that this extra fraction reflects a metabolic disturbance.

References

1 BERGSTRÖM, K. Personal communication.

PAPER V

Myocardial Infarction and an Extra Pre-beta Lipoprotein Fraction

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The aim of the screening procedure in our population study (II) was to identify subjects with high risk of ischemic heart disease and to modify the risk factors. High serum cholesterol and triglycerides belong to the major risk factors (7 8, 11) The correlation between high prevalence of a pre-beta-1 fraction and angina pectoris suggests that the pre-beta 1 fraction might be risk factor also for developing myocardial infarction. Thus an examination of the occurrence of the extra pre beta band of the electrophoresis in patients with a history of myocardial infarction was performed.

Serial analyses of the lipoproteins have shown that the pre-beta 1 fraction often occurs at a certain time after a meal (IV) In order to standardize the examination conditions a special test meal was used in the study of patients with a history of acute myocardial infarction (MI) and of healthy control subjects.

Material

Patients with MI This group consisted of 20 men with a mean age of 55 7 years (Table I) They constitute the majority of middle aged men

TABLE I Some anthropometric data, ECG code, physical working capacity and cardiac drugs in 20 patients with history of myocardial infarction

Initial	Age yrs	Height cm	Weight kg	ECG code	Physical working capacity kpm/min	Nitroglycerin (N) Digitalis (D) Beta-blockers (B)
B F	56	179	71	1—1—1	1000x	—
B G	60	183	78	1—1—6	600	N, D
B L	56	179	96	1—1—4	600	D B
B A	57	178	81	1—1—4	300	N, D
D S	47	163	74	1—2—4	400	B
E S	50	173	80	4—1 5—2	600	N, D B
E O	51	178	75	—	800x	N
G R	47	171	68	1—2—4	900	—
J A	65	175	77	1—1—4	200	N
J A	61	171	66	1—2—4	300	N D
J B	55	184	85	1—1—1	1200	D B
K M	58	183	82	4—4, 5—4, 8—1	600	N, B
L E	58	176	82	1—1—1	600x	N
L K	53	164	65	8—1	200	B
L Y	57	174	68	—	1100	N
M B	54	177	78	—	500	N, B
N R	55	179	91	1—1—4	1000	—
P A	59	174	65	1—3—4	1000	—
S R	51	165	67	—	600x	—
Ö O	52	165	64	—	800	N
Mean	55 7	175	73 7		665	(x=estimated value)

with MI regulary checked at the clinic of Internal medicine and living in Boden. Three of them had had two myocardial infarctions and the others had had one since 1962. Four patients had their MI in the course of the last year but none of them less than five months before this examination. The WHO criteria for the diagnosis of definite acute MI were used for the most recent MI (12). Twelve patients had at the time abnormal Q and QS patterns in ECG. Seventeen patients were suffering from angina pectoris of effort and eleven of them were treated with nitroglycerin. Six patients were treated with digitalis and seven with beta receptor blocking drugs. Some anthropometric data, the ECG code and the physical working capacity are given in Table I.

Controls. This group consisted of 8 men 57—60 years old from the population study (II). They were chosen at random from among subjects with a certain date of birth (5, 10 and 25) after those with symptoms of angina of effort or other arteriosclerotic diseases, abnormal ECG or a history of diabetes and gall-stone had been excluded. All the controls were fully employed.

Methods

The patients and the control subjects were asked to come to the laboratory in the morning. After blood sampling a *test meal* was given. The procedure has been described in paper IV. The methods for the *electrophoresis of lipoproteins* and serum lipids analyses have been described in a previous paper (I).

The Minnesota code (3) was used for *ECG coding*.

The Fisher exact probability test (10) was used to test the significance of differences.

Results

Serum lipids

MI patients. Five out of 20 patients had both high serum cholesterol and triglyceride values. One had a high cholesterol value only and four had a high triglyceride value only. The remaining ten patients had normal serum lipids (Table II).

TABLE II. Cholesterol and triglyceride values, type of hyperlipoproteinemia and occurrence of pre beta-1 fraction after overnight fasting and 8 hours after test meal in 20 patients with history of myocardial infarction.

	After overnight fasting				8 hours after test meal		
Initial	Cholesterol mg%	Triglycerides mmol/l	Type	Pre-beta-1	Cholesterol mg%	Triglycerides mmol/l	Pre beta 1
B F	261	1,2	0	—	255	1,3	—
B G	241	4,4	IV	?	236	3,6	—
B L	224	4,2	IV	+	230	4,8	+
B A	213	4,0	IV	+	270	3,9	?
D S	317	1 7	0	+	225	0,8	—
E S	401	3,2	IIB	—	446	3,9	—
E O	203	2,0	0	?	210	1 7	+
G R	351	1,3	IIA	—	363	1,9	+
J A	291	1 7	0	—	308	2,2	—
J A	308	2,1	0	+	300	2,1	+
J B	171	1 3	0	—	185	1,2	—
K M	329	2,2	IIB	+	329	1,8	+
L E	327	3 3	IIB	+	353	3,6	+
L K	368	3,5	IIB	+	377	5,0	+
L Y	268	1,9	0	—	285	1,6	—
M B	306	4,0	IV	—	321	3 7	?
N R	336	4,0	IIB	+	342	4,9	+
P A	295	1,2	0	+	300	1,3	+
S R	303	1 4	0	+	312	1,6	+
O O	258	1 3	0	—	266	1 4	+
m	279	2,50			29[illegible]	2,52	

C ntrols Seven out of eight control subjects had normal cholesterol and triglyceride values. One had a high triglyceride value.

Hyperl poproteinem

All pat ents Ten out of the 20 patients had hyperlipoproteinemia. One had a Type II A pattern, five had a Type II B pattern and four had Type IV hyperlipoproteinemia (Table II)

Controls A Type IV pattern was found in one of the eight control subjects. The rest of them had a normal lipoprotein pattern

This d fference in occurrence of hyperlipoproteinemia between the MI patients and the control subjects is not statistically significant (p=0 069)

Pre-beta-1

All patients After overnight fasting 10 out of 20 patients had a pre-beta 1 fraction on the electrophoresis and eight more had no detectable pre beta 1 fraction In two patients it was not possible to interpret the electrophoresis due to the presence of broad pre-beta band (Table II) After the test meal 11 patients had a pre-beta 1 fraction while seven had no extra pre-beta band. Again two of the electrophoresis patterns were not possible to interpret (Table II) In all, 13 patients had the extra fraction after overnight fasting and/or after the test meal F e patients had no pre-beta 1 on either occasion. In the remaining two patients it was not possible to interpret the electrophoresis (cf II) One of them had had an extra pre-beta band at a previous examination. These two cases are withdrawn from the comparison with the controls

In all 15 MI patients had a hyperlipoproteinemia and/or a pre-beta-1 fraction. In f ve out of these a pre-beta 1 fraction was present without a concomittant l poproteinemia.

Controls One of the eight control subjects had pre-beta-1 fraction *after overnight fasting* and also eight hours after the test meal One more control subject had pre-beta-1 after the test meal. Six of the controls had no detectable pre-beta-1 fraction on either occasion. The man with high triglyceride value had no pre-beta 1

The difference in occurrence of a pre-beta 1 fraction between the MI patients and the control subjects is statistically significant (p=0,31)

There were no correlations between the occurrence of pre-beta 1 and Q and QS pattern in ECG angina of effort, physical working capacity or treatment with cardiac drug respecti ely

Discussion

In a previous paper (IV) it was shown that the pre-beta 1 fraction may not always appear within 6—8 hours after a meal. This was particularly true in patients with high serum lipids. It was proposed that blood samples should be taken in the morning after overnight fasting (about 12 hours after the eveni g meal) and also 8 hours after the test meal. By this improved technique an extra fraction was found in even more MI patients.

About two thirds of MI patients in this small group had the pre beta 1 fraction. The corresponding proportion among patients with typical or suspected angina pectoris was about one half (II) This number would probably be higher if the latter group of patients had been examined by the new improved technique.

In the small group of control subjects two out of eight had a pre-beta 1 fraction. A similar frequency has been observed in a group of younger control subjects from our laboratory staff and in a group of medical students (2) Around 14% of the men from the population study (II) with no typical or suspected angina pectoris had the pre beta 1 fraction Again, this number would probably be somewhat higher in studies under the new standardized conditions

Half the number of MI patients had hyper lipoproteinemia, Type II A, II B or IV These data on the occurrence of hyperlipoproteinemia in MI patients are in accordance with findings reported by Enger & Ritland (5) and Gustafson et al. (6)

There was no statistical difference in the occurrence of hyperlipoproteinemia between the MI patients and the control subjects. However a significant difference between the two groups was found in the occurrence of a pre-beta 1 fraction It is interesting to notice that five out of 20 MI patients in this study had a pre-beta 1 but normal serum lipids. It appears as if this technique of lipoprotein electrophoresis might give additional information regarding the lipid metabolism in subjects with normal cholesterol and triglyceride values.

Preliminary data from our population study has shown that in the pre-beta 1 group about the same proportion of subjects has the regular risk factors (high cholesterol, high blood pressure and a smoking habit) as in the group with no extra pre-beta fraction in the electrophoresis.

There are evidences showing that pre-beta 1 is a pre-beta lipoprotein of high density The existence of such a fraction has recently been reported by Ellefson et al. (4) Their fraction consisted mainly of cholesteryl esters, cholesterol, phosphatidyl cholines and sphingomyelins. Only traces of triglycerides were observed. Pre-beta-1 may also be identical with Berg's Lp antigen (1) and the so-called sinking pre-beta lipoprotein (9)

No explanation for the correlation between ischemic heart disease and the pre-beta 1 fraction has been given This extra fraction may in some way be either a factor involved in the development of ischemic heart disease or reflect a disorder induced by the diseased heart. The occurrence of the pre-beta 1 fraction among subjects with no symptoms of ischemic heart disease is too high, which makes the latter explanation less likely and the former proposition more probable. In that case pre-beta 1 should be looked upon as a risk factor. It is however too early to state this definitely We hope that data from our population study will give us further information concerning the matter in question in the future

At present we also need more information regarding other factors than meals that can cause pre-beta 1 fraction to appear on the electrophoresis

Summary

A group of 20 patients with a history of myocardial infarction and a group of eight healthy control subjects have been examined with lipid analyses in connection with a test meal. Half the number of the patients had hyperlipoproteinemia as opposed to one of the eight control subjects. The electrophoreses were possible to interpret with respect to an extra pre-beta fraction in 18 MI patients. Thirteen of these patients had the extra pre-beta fraction as opposed to two of the controls. This difference is statistically significant. It is proposed that the pre-beta 1 fraction might be another risk factor for ischemic heart disease

References

1 BERG K., A new serum lipoprotein system in man — the Lp system. Acta path. microbiol. scand. 59. 369 1963.

2. BERGSTRÖM, K., Personal communication.

3 BLACKBURN H KEYS, A SIMONSON E RAUTAHARJU P & PUNSAR, S The electrocardiogram in population studies. A classification system. Circulation 1 1160 1970

4. ELLEFSON R. D., JIMENEZ, B. J & SMITH, R. C. Pre-beta (or alpha-2) lipoprotein of high density in human blood. Mayo Clin Proc 46. 328, 1971

5 ENGER, S C & RITTLAND S. Serum lipoprotein pattern in myocardial infarction Acta med scand 187 333, 1970 —— Not correct

6. GUSTAFSON,A., ELMFELDT,D WILHELMSEN L. & TIBBLIN G. Serum lipids and lipoproteins in patients after myocardial infarction compared to random population sample (To be published)

7 KANNEL, W B CASTELLI, W P GORDON T & McNAMARA, P N., Serum cholesterol, lipoproteins, and the risk of coronary heart disease. Ann. Int. Med 74 1 1971

8. KEYS A. Diet effects on the blood lipids in man. Medizinische Prisma (C. H Boehringer Sohn, Ingelheim am Rhein) 3 1967

9 RIDER, A. K LEVY R I & FREDRICKSON, D S "Sinking" pre-beta lipoprotein and the Lp antigen. Circ 42. Suppl III 10, 1970

10 SIEGEL, S Nonparametric statistics for the behavioral sciences McGraw-Hill Co Tokyo 1956.

11 WILHELMSEN L. & TIBBLIN, G Physical Inactivity and Risk of Myocardial Infarction — The Men Born in 1913 Study In Coronary Heart Disease and Physical Fitness Eds MALMBORG, R. O & ANDREE LARSEN, O Munksgaard, Copenhagen 1971

12 Working Group on Ischemic Heart Disease Registers WHO, Copenhagen 1968

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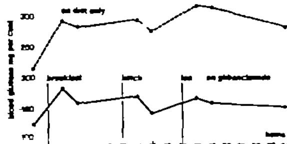


Fig 1. Blood glucose profiles throughout the day in 26 patients on diet only and then following therapy with glibenclamide at breakfast.

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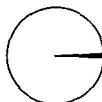
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Bibliography.

Andersson, B, Fagerberg S.-E & Lennerhagen, P Klinisk prövning av DAONIL (glibenclamid — HB 419) — ett nytt peroralt antidiabeticum. Läkartidningen 68 Suppl II (1971)

Bhatia, S K et al. Glibenclamide Therapy in Diabetes Mellitus Brit med J 2, (1970) 570—572

Engelbert, K, & Kief H Morphological findings in rat islets after administration of new highly effective sulphonylurea-derivate 3rd Capri Conference, Acta Diabetologica Latina (1969) 275

Haddon, R. et al Long-term Experience with Chlorpropamide in Diabetes Mellitus Diabetes 11 (1962) 91—95

HB 419 Tegernsee-Konferenz über das neue orale Antidiabetikum HB 419 1969

Loubatières A et al Experimental Study of New Highly Active Hypoglycaemic sulphonamide, Glibenclamide Diabetologia, 5, (1969) 1

Loubatières, A et al Effect of particularly active sulphonylurea, glibenclamide, on the development and neogenesis of the pancreatic islets of Langerhans C. R. Acad. Sci, 267 (1968) 238

Mehnert F & Karg E Glibenclamide new oral antidiabetic agent, Deutsche Med Wschr 18, (1969) 819

Muller R et al A new Oral Antidiabetic Drug Horm and Metab Res Suppl ed Vol 1 (1969) 88

O'Sullivan, D J & Cashman W F Blood Glucose Variations and Clinical Experience with Glibenclamide in diabetes mellitus Brit med J 2, (1970) s. 572—574

Pfeiffer E F Acta diabet lat 6 (1969) 477

Raptis S et al Horm and Metab Res Suppl ed Vol 1 (1969) 65—72

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ADRENERGIC RECEPTOR RESPONSE IN HYPOTHYROIDISM

an in Vitro Study on Human Adipose Tissue and Rabbit Aorta

By

Urban Rosenqvist

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ADRENERGIC RECEPTOR RESPONSE IN HYPOTHYROIDISM

An in itro study on human adipose
tissue and rabbit aorta

by

URBAN ROSENQVIST

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II Noradrenaline induced lipolysis in subcutaneous adipose tissue from hypothyroid subjects The relation of noradrenaline response to the degree and duration of the disease
Rosenqvist U
Acta med scand. in press

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INTRODUCTION

The biological effects of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) show many similarities with those produced by the catecholamines Thus, patients with thyrotoxicosis have tachycardia, increased sweating and an irritable mental state Similar symptoms may be present in subjects with a catecholamine-producing tumour The hypothyroid state on the other hand, is characterized by slow mental and motor functions and decreased sweating depletion of catecholamine stores by treatment with reserpin causes similar symptoms (29) It has also been noted that patients with thyrotoxicosis react to adrenaline administration with more severe tachycardia than euthyroid subjects (30)

Such observations ha e led to the assumption that the actions of catecholamines and thyroid hormones may be interrelated (for reviews see 40 63, 90) but the precise nature of this relationship is not clear Two p incipal explanations have been advanced

- thyroid hormones may control the metabolism of catecholamines
- thyroid hormones may modulate the adrenergic receptor sensiti ity

Thyroid Ho mones and Cat ch lamine Metabolism

A great number of studies has been reported regarding the effect of thyroid hormones on catecholamine metabolism However the results are in many aspects contradictory

Effect of the hyperthyroid state The excretion of catecholamines was not modified in adult thyrotoxic patients (39 56 67 92) Furthermore the release of catecholamines on tilting was significantly lower in hyperthyroid than in control subjects (39) and less catecholamine was liberated in hyperthyroid subjects during hypoglycemia (39)

The tissue content of noradrenaline was increased in myocardium from thyrotoxic rats while a decreased content was found in the adrenals (45) Measurements of monoaminoxidase (MAO) activity gave decreased values in thyrotoxic subjects (67) The amounts of catechol-O-methyltransferase (COMT) activity did not seem to be significantly altered in hyperthyroid rats or humans (46 92 93)

Effect f the hypothyroid state Normal (64) or increased (56 92) excretion of catecholamines in urine has been observed in patients with hypothyroidism Increased val es were also found in hypothyroid monkeys under standardized conditions (28) Less catecholamine was liberated during insulin-induced hypoglycemia in hypothyroid subjects than in controls (64) while cold stress induced a much more pronounced urinary excretion of catecholamines in hypothyroid than in control rats (50 68) Heart muscles from hypothyroid rats contained decreased amounts of noradrenal

ine while the content of adrenaline was enhanced (45) Furthermore the hypothyroid state was accompanied by an accelerated turnover of ^{3}H-noradrenaline in the heart muscle of rats (53) Increased monoaminoxidase activity was observed in jejunal biopsies from hypothyroid subjects (67) while decreased values were found in the liver of hypothyroid rats (93) The amount of COMT activity did not seem to change in hypothyroid subjects (46)

Obviously it is difficult to interpret all these findings regarding catecholamine metabolism during hyper- or hypofunction of the thyroid gland. They might be due to the use of different assay techniques for catecholamines and to the fact that large variations might exist within and between species and organs The above mentioned changes in catecholamine metabolism might, however also reflect events secondary to a modified adrenergic receptor response (44)

Thyroid Hormones and Adrenergic Receptor Function

The possibility that thyroid hormones could change the sensitivity of the adrenergic receptors to catecholamines was discussed already in 1908 (25) and has since been demonstrated by several investigators (for review see 40 63 90) Some authors (4 15 72) were however unable to show such an interrelation and a critical review of the subject was recently published (66)

The idea that T_4 or T_3 may modify the adrenergic receptor response to catecholamines differentially in different autonomic neuroeffector systems was first formulated by Aumann and Youmans (7) These authors demonstrated that administration of thyroid hormone to rabbits increased the chronotropic effect of adrenaline on the heart, while the response of intestinal smooth muscle to the catecholamine remained unaffected. They concluded that thyroid hormones may exert different effects on the adrenergic receptors of different tissues

Ahlquist s classification of adrenergic receptors into the alpha and the beta type (2) made it possible to analyse the interaction between catecholamines and thyroid hormones in greater detail. Zsotér et al. (94) using the hind limb technique in normal and thyrotoxic dogs demonstrated that the vascular response to noradrenaline and adrenaline was abolished by thyroid hormone administration The vessels however retained their sensitivity to angiotensin The contractile response to the catecholamines could be restored by blocking the beta adrenergic receptors The authors concluded that "thyroid hormones increase only the sensitivity of beta adrenergic receptors to catecholamines or increase their sensiti ity relatively more than that of the alpha receptors Similar observations on muscle blood flow in man (81) support these conclusions

The effect of thyroid hormone on smooth muscle response to noradrenaline has also been examined in vitro. Thus MacMillan and Rand (70) found that the maximal noradrenaline response of aortic strips from rabbits was enhanced in the hypothyroid state They did not test other agonists or antagonists and it cannot be determined from their data whether there was a specific increase in alpha-adrenergic response or a generalized enhancement of the contractile response

The interrelationship between thyroid hormones and the lipolytic action of noradrenaline was first tested in rhesus monkeys in vivo (31) It was shown that a decrease in the thyroid-hormone level was accompanied by a diminish-

ed lipolytic response to noradrenaline infusions Similar results were later obtained in human subjects (38) although the findings seemed to be less consistent (35) Furthermore it was dem onstrated that the concentration of plasma glycerol was increased in hyperthyroid subjects while hypothyroid patients showed normal lev els (62)

The interaction between catecholamines and thyroid hormones regarding lipolysis was further studied in itro by Debons and Schwartz (19) They demonstrated a marked decrease in the adrenaline response of adipose tissue from hypothyroid rats but showed an enhanced response of tissue from thyrotoxic animals Bray (11) confirmed this finding of a decreased lipolytic response to adrenaline in vitro but was unable to establish whether it was due to increased alpha adrenergic or decreased beta adrenergic activity Later Krishna et al (54) demonstrated that the diminished lipolytic effect of catecholamines in adipose tissue from hypothyroid rats was caused by a reduction in the amount of the enzyme adenyl cyclase. Furthermore administration of high doses of T_4 for five days markedly stimulated the synthesis of adenyl cyclase in normal rats

Vaughan tested the in vitro effect of T_3 on the lipolytic response to adrenaline of fat pads from hypothyroid rats (89) A three-hour preincubation with T_3 was needed before an increase in the response to adrenaline could be measured. Since no effect of T_3 was observed on the lipolytic action of submaximal concentrations of theophylline in normal rat adipose tissue the stim latory action of the hormone was probably ot due to inhibition of the specific cyclic AMP phosphodiesterase as had been suggested by Mandel and Kuehl (71) but to an increased adenyl-cyclase response Challoner and Allen (16) were in fact able to demonstrate enhancement of the adenyl-cyclase response to adrenaline by T_3 added in vitro to fat cells from normal rats The addition of puromycin or cycloheximide blockers of protein synthesis could not inhibit the effect of T_3.

Since the responses of the alpha and beta adrenergic receptors oppose each other in sev eral organs (2) the finding that adenyl-cyclase activity is decreased in hypothyroidism could als have been the result of an enhanced alpha-receptor response However Bray (11) was unable to modify the catecholamine-induced lipolysis in hypothyroid rats with alpha-adrenergic agents This negative finding might have been due to the fact that phentolamine the alpha adrenergic blocker used, exhibits antilipolytic activity in rat adipose tissue (42)

Human adipose tissue contains both alpha and beta adrenergic receptors with opposite actions on lipolysis (23) The influence of thyroid hormones on the regulatory function of these receptors as regards lipolysis in man has not been studied previously

The purpose of the present study was

1 to analyse the effects of a decrease in thyroid hormone concentration on the adrenergic receptors in adipose tissue from man
2. to elucidate the mechanisms that trans mit the alpha-adrenergic response in human adipose tissue
3 to study the validity of the results obtained in hypothyroidism in man Smooth muscle from rabbit was used as another model of alpha-adrenergic receptor response.

PATIENT MATERIAL

The total number of subjects studied was 92 Of these 48 had developed hypothyroidism after radioiodine treatment for thyrotoxicosis Six subjects were hypothyroid secondary to Hashimoto s disease and one became hypothyroid after total thyroidectomy for cancer of the gland

The control group consisted of 32 previously hypothyroid subjects on replacement therapy with thyroid hormones Of these patients 14 were studied before and during therapy Five subjects were considered to be mildly hypothyroid on clinical grounds in spite of normal values for TSH in serum. These patients were included only in one section of the studies (Paper II) Detailed information on the patient material is given in Papers I V

The nature purpose and possible risks involved in the procedure were explained to the subjects prior to obtaining their informed consent. No reward was given for their participation in this study

METHODS

Human Adipose Tissue

The catecholamine-induced lipolysis in human adipose tissue has been thoroughly investigated in vitro in tissues from normal subjects and the experimental procedure has been described in detail (23) The lipolytic effect of the catecholamines is mediated by beta-adrenergic receptors enhancing the formation of cyclic AMP which, in turn, stimulates the hormone-sensitive lipase as illustrated in Fig 1 (23, 37 78 79) Alpha-adrenergic stimulation on the other

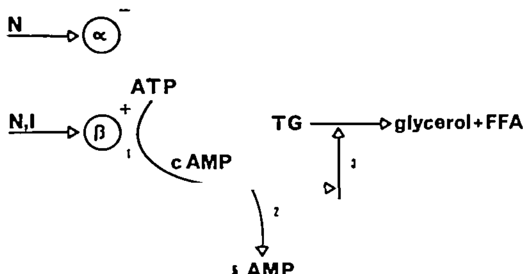


Fig 1 Schematic drawing illustrating the mechanism which regulate lipolysis in human adipose tissue Abbreviations used N = l-noradrenaline I = l isopropylnoradrenaline ATP = adenosine triphosphate cAMP cyclic 3 5 adenosine monophosphate 5 AMP = adenosine monophosphate TG triglycerides FFA = free fatty acids
(α) denotes a hypothetical alpha adrenergic receptor which inhibits ( ) lipolysis
(β) denotes a hypothetical beta adrenergic receptor which stimulates ( ) lipolysis
The different enzymes involved in the depicted system are 1) adenyl cyclase 2) phosphodiesterase 3) lipase.

hand diminishes the rate of lipolysis (23) by an unknown mechanism (37) Hence the lipolytic effect of noradrenaline which is a combined alpha and beta adrenergic agonist, is less than that of isopropylnoradrenaline which is an almost pure beta adrenergic agonist. The catecholamine-induced lipolysis is therefore also inhibited by propranolol which blocks the beta-adrenergic receptor while phentolamine which is an alpha-adrenergic antagonist stimulates noradrenaline-induced lipolysis Cyclic AMP is degraded intracellulary by the phosphodiesterase enzymes and the activity of these enzymes can be blocked by theophylline This agent is therefore a potent lipolytic substance in adipose tissue Lipolysis is also stimulated by dibutyryl cyclic AMP which readily enters the adipose cells and mimics the effects of endogenously produced cyclic AMP

Subcutaneous adipose tissue was obtained by surgical biopsy from the thigh of non-fasting subjects The tissue was excised under local anaesthesia using 3-5 ml of prilocain chloride Citanest® Care was taken to minimize traumatization of the specimens About 3-6 g of adipose tissue were regularly obtained and transported to the laboratory in 0 9% NaCl at 37°C

The use of a local anaesthetic might have introduced a systematic error in the response to different lipolytic agents Thus Östman and Arner (97) demonstrated that prilocain chloride may reduce both basal and stimulated lipolysis However the responses to noradrenaline isopropylnoradrenaline dibutyryl cyclic AMP and theophylline were all reduced in a similar way This indicates that the above anaesthetic might have a general antilipolytic effect but does not preferentially decrease the response to, e g noradrenaline by enhancing the alpha adrenergic response Thus the use of prilocain does not influence the results in qualitative way

Isolated fat cells from human subcutaneous adipose tissue were prepared according to Smith (82) Special care was taken to minimize traumatization of the cells by using freshly siliconized glassware The collagenase digestion of the tissue and the incubations of the cells were performed at 37°C in Krebs-Henseleit bicarbonate (KHB) buffer pH 7 4 (16) containing 4% bovine albumin and 1 mg/ml glucose The concentration of cells was calculated from determination of cell size and the triglyceride content of the sample (82)

Measurement of lipolysis The adipose tissue was preincubated wihtout glucose for 60 min at 37°C in KHB buffer pH 7 4 containing 1% bovine albumin This preincubation allows the FFA and glycerol of the specimens to equilibrate with the medium as described in detail (95) Separate tissue sections (50-100 mg) were transferred from the preincubation medium to 1 5 ml KHB, pH 7 4 containing 3% albumin and 1 mg/ml glucose The incubations were carried out for two hours in polyethylene vials at 37°C using air as gas phase The method of incubation has been investigated previously in detail by Östman (95) The use of 3% albumin is important since it binds the liberated FFA which might otherwise accumulate in the cells and inhibit lipolysis probably by inhibiting the formation of ATP (3) The same concentration of glucose was used as in previous studies of the catecholamine response of normal adipose tissue (23)

Under the above conditions the rate of basal as well as stimulated lipolysis is constant for at least two hours in normal adipose tissue (23) The release of glycerol was used as an index of lipolysis This is a better measure of lipolysis than accumulation of FFA

Table I Analysis of the precision of the method for adipose tissue incubation and determination of glycerol release

Group	N	Mean of duplicate determinations	Glycerol release (µmoles/g ww/2 h) S D of mean	S D (% of mean)
1	154	0 444	± 0 228	± 51 4
2	163	1 424	±0 265	± 18 6
3	114	2 437	±0 406	± 16 7
4	96	3 826	± 0 901	± 23 6

since glycerol, in contrast to FFA is utilized by the tissue only at a minimal rate (10). The amount of glycerokinase which is limiting for the reutilization of glycerol is very low in normal adipose tissue, and could phosphorylate only 2 % of basal and 0 9 % of stimulate glyce ol release (52)

Mono- and diglycerides may accum late during the incubation of adipose tissue and the values for glyce ol may therefore underestimate the real rate of lipolysis induced by the hormone-sensitive lipase. Determinations of mono- and diglycerides during a two-hour incubation have shown however that the amounts are extremely low and do not significantly influence the rates of lipolysis determined by measuring glycerol alone (6)

Glycerol was determined according to the method of Wieland (91) as modified by Larsen (61)

All values of glycerol release were related to the wet weight of the samples The composition of the tissue might diff r between control subjects and patients with hypothyroidism as regards to, g protein and lipid content. Therefore differences in absolute values of basal or stimulated lipolysis could represent either real changes in the rate of lipolysis or reflect variations in the composition of the tissue For this reason, the absolute rates of glycerol release were not compared between the two groups of subjects only the patterns of response to different agents were evaluated.

The precision of the method of incubation and analysis of glycerol was calculated from duplicate incubations. The standard deviation of the mean of the duplicate measurements was calculated from the formula (34)

$$\frac{1}{2}\sqrt{\frac{\Delta \times \Delta}{N}} \quad \text{where}$$

Δ is the difference between two determinations and N the number of duplicate determinations

The difference between duplicates was separately estimated from samples with low medium high and very high concentrations of glycerol The results are shown in Table I. The standard deviation was around 20 % of the mean. When, however low concentrations of glycerol were analysed, it reached 51 4 %. This high S D value was probably due to the poor precision of the spectrophotometer when low values for optical density are read (31)

Measurement of adenyl cyclase activity Adenyl-cyclase activity was measured both in fat pads and isolated fat cells The method described by Ku and De Renzo (55) for

the assay of cyclic AMP formation was used with some modifications (Paper IV) Since the original procedure is insufficient for the separation of small amounts of labelled cyclic AMP (53) three paper chromatography steps (22) were added to the original technique for the isolation of labelled cyclic AMP from other labelled compounds (Paper VI) The paper chromatography procedure described by Douša and Rychlík (22) is very efficient for this purpose and the modification employed improved the results (33)

The method of Kuo and De Renzo measures the activation of adenyl cyclase under the assumption that the specific activity of the ATP pool remains constant during the incubation. This seems to be the fact since comparison of the method of Kuo and De Renzo with measurements of unlabelled cyclic AMP by the protein kinase method has shown good agreement (65)

All calculations of glycerol release precision of the incubation procedure and quench correction were performed on a PDP 8L computer

Smooth Muscle from Rabbit Aorta

The adrenergic receptors of rabbit aorta have been extensively characterized and it is known that adrenaline has a marked alpha-adrenergic property in the tissue while the beta-adrenergic response is weak (27) Hence this tissue was used for further study of the effect of hypothyroidism on the alpha-adrenergic response

Eight rabbits were made hypothyroid by subcutaneous injection of 10 mC of ^{131}I 8 10 weeks prior to the experiments The same number of control animals was used. The effect of radioiodine treatment was apparent both from the reduced gain of weight and the significantly lower PBI values in the hypothyroid group Helical strips of the aortic tissue were prepared and mounted in 20 ml overflow cuvettes containing Tyrode solution at 37°C (Paper VI) The isometric contractile responses to adrenaline and histamine were recorded by the cumulative dose-response curve technique which means that concentration of the agonist was increased by subsequent additions to the medium (88) The responses to histamine and K^+ were also measured in order to test the reactivity of the contractile system to agonists which do not act via adrenergic receptors The contractile response to K^+ was measured at the beginning and at the end of each experiment and no significant changes were observed.

The calcium content of the aortic tissue was determined by the atomic-absorption technique (77) and related to the wet weight of the specimens The use of wet weight might have introduced a systematic error since the water content of the tissues from the hypothyroid animals might have been increased (84) The calcium content of the latter specimens tended to be lower than in those of the controls (3 50 ± 0 70 and 4 10 ± 1 28 mmol/kg ww Mean ± S E M) but this difference was not significant. Furthermore it should be mentioned that the method of determination of tissue calcium is not very precise (8) and minor changes of calcium content therefore may have escaped detection.

Drugs

All concentrations of the different agonists are given in terms of the free base

RESULTS

The main finding of the present study was an augmented alpha-adrenergic response in subcutaneous adipose tissue from hypothyroid subjects (Paper I V) This enhanced response completely inhibited the noradrenaline-induced formation of cyclic AMP in this tissue (Papers I IV) Furthermore the alpha-adrenergic respons was similarly enhanced in a rtic strips from hypothyroid rabbits (Paper VI)

In the following a detailed account of the results will be given

Studies on Adipose Tissue

The enhanced alpha-adrenergic receptor function in adipose tissue from hypothyroid subjects caused a marked decrease in the lipolytic response to noradrenaline in vitro (Paper I) This occurred already after 1 5-2 months of the disease and was corrected by replacement therapy (Paper II). The response to noradrenaline was neither influenced by age or body weight, nor by the duration of the disease or the length of treatment. Hence no further subdivi ion of the two groups of subjects seemed justified (Paper II).

An attempt was made to correlate the de rease in lipolytic response to noradrenaline to the diff rent parameters used for evaluation of thyroid function in man (Pape II) Resin uptake of T_3 howed a correlation but PBI, TSH cholesterol and thyroidal uptake of radioiodine were insignificant.

Isopropylnoradrenaline dibutyryl cyclic AMP and theophylline significantly stimulated lipolysis in adipose tiss e from both control and hypothyroid subjects (Papers I and II)

The lipolytic effect of noradrenaline in adi pos tissue from hypothyroid subjects was im mediately restored by phentolamine which blocks the alpha-adrenergic receptor function (Pape I) Phentolamine alone did not signifi cantly influence basal glycerol release (Paper III)

Contrary to previous observations in normal human adipose tissue (24) it was found that prostaglandin E_1 (PGE_1) enhanced rather than decreased the response to noradrenaline in adi pose tissue from hypothyroid subjects while it inhibited the response to isopropylnoradrenaline (Pape V).

The mechanism by which the alpha-adrenergic receptor influences lipolysis was studied in more detail The results obtained, using glyc rol release as an indirect measure of the level of cyclic AMP showed that activation of the alpha receptor decreased the level of cyclic AMP (Pape III) In addition, direct measurements of cyclic AMP formation demonstrated that the alpha-adrenergic receptor indeed acted by inhibiting adenyl-cyclase activity (Paper IV) Thus in sections from adipose tissue as well as in isolated fat cells from hypothyroid subjects noradrenaline was able to stimulate adenyl cyclase only in the presence of phentolamine

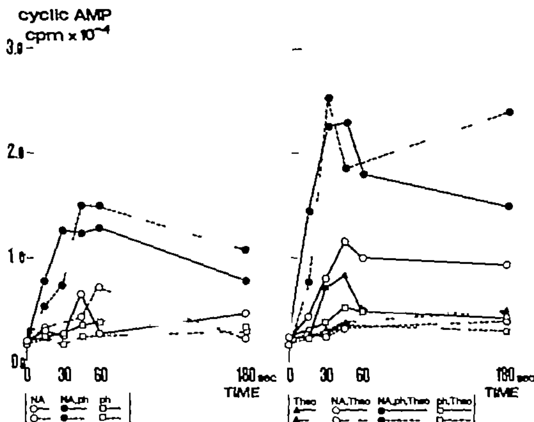


Fig 2 Formation of radioactive cyclic AMP in fat cells from normal subcutaneous adipose tissue on short time (15-180 sec) stimulation with 2 x 10^{-5} M l-noradrenaline (NA) in presence or absence of 5 μg/ml phentolamine (ph) at 37°C in KHB buffer containing 4 % albumin, 1 mg/ml glucose and without (left) or with (right) 10^{-3} M theophylline (Theo) The incubations were stopped by addition of perchloric acid final concentration was 3 %. The results of two different experiments are shown (I ——— II ------) The concentration of adipose cells was 0 7 and 0 6 x 10^6 cells/ml respectively The values of cyclic AMP have been corrected for recovery

whereas in adipose tissue pads from euthyroid subjects noradrenaline by itself was a potent activator of the enzyme

The effect of noradrenaline on adenyl-cyclase activity in adipocytes from hypothyroid subjects was not significantly influenced by the simultaneous addition of T_3 (Paper V)

The effect of short time (15-180 sec) stimulation of cyclic AMP formation by noradrenaline was studied in fat cells isolated from normal human subcutaneous tissue Noradrenaline (0 2 x 10^{-5} M) alone exerted a small stimulatory effect while the addition of phentolamine markedly augmented this response The stim

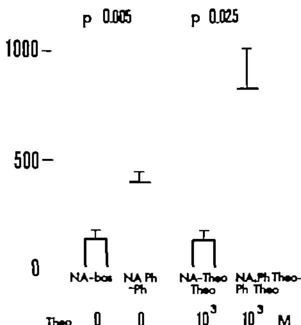


Fig 3 Accumulation of radioactive cyclic AMP in isolated fat cells from normal subcutaneous adipose tissue incubated for 30 sec with 3×10^{-5} M noradrenaline (NA) in presence or absenc of 5 µg/ml phentol amin (ph) in KHB buffe containing 4 % albumin and 1 mg/ml glucose with or without 10^{-3} M theophylline (Theo) The incubations were stopped by bioling for 3 minutes The p values were calculated from the mean dif f rence between cells incubated in presence r absenc of phentolamine The results are the mean of four experiments

ulatory effect of phentolamine was evident al ready after 15 sec of incubation and maximal rate of cyclic AMP formation was obtained within the first 45 sec The addition of theophylline did not markedly change the relationship between the response to noradrenaline and that to noradrenaline + phentolamine (Fig 2) These results were confirmed in a separate series of experiments (Fig 3)

Studies on Smooth Muscle

Studies on smooth muscle from aortas of hypothyroid rabbits were performed in order to determine whether enhancement of the alpha-adrenergic response lso occurs in tissues other than human adipose tissue (Paper VI)

Aortic strips from hypothyroid animals dem onstrated enhanced response to alpha-adrenergic stimulation Thus the contraction induced by adrenaline was significantly strong- e in the hypothyroid than in the control group while the dose producing 50 % of maximal contraction (ED_{50}) was the same in tissues from both groups On the other hand, the two kinds of rtic strips did not differ in their response to either histamine or K^+

The enhanced alpha-adrenergic response of the aortic strips from hypothyroid animals was not modified by the presence of lanthanum (La^{+++}) in the medium (Paper VI)

The total calcium content of the aortic tissue from the two groups did not differ signifi cantly whethe the specimens were examined directly afte excision or 60 minutes after incubation in a Tris buffer ontaining 1 5 mM $CaCl_2$ or 2 mM $LaCl_3$ (Paper VI) It was noted however that La^{+++} displaced more calcium from the control tissue ($p < 0$ 01) than from the tissue of the hypothyroid animals ($p > 0$ 05) (Paper VI)

DISCUSSION

The present investigation was undertaken in order to determine whether the previously described interactions between catecholamines and thyroid hormones occur at the adrenergic receptor level The results show that a decrease in thyroid hormone production is accompanied by enhancement of the alpha-adrenergic receptor response in human adipose tissue and rabbit aorta.

Subcutaneous adipose tissue from patients with hypothyroidism does not respond to noradrenaline with an increase in lipolysis as it does from euthyroid subjects The reduction of the noradrenaline response was a relatively early derangement in the course of the disease and was readily restored within 1 5-2 months of replacement therapy (Paper II) This was true whether different subjects were used in the control and hypothyroid groups or if the same individuals were studied both before and after treatment. The rather rapid recovery of the noradrenaline response is in contrast to that of another metabolic disturbance in hypothyroidism namely the decreased rate of free water reabsorption by the kidneys More than a year of thyroid replacement therapy was needed before complete recovery of this function was obtained (21)

An attempt was made to relate the decrease in noradrenaline response to the degree of hypothyroidism in the present patient material A correlation ($p < 0.05$) was found with the resin uptake of T_3 but no significant correlation was obtained with other parameters of thyroid function (Paper II) These findings indicate that most of routine laboratory tests of thyroid function do not reflect the degree of hypothyroidism in the adipose tissue

By studying subcutaneous adipose tissue in vitro it was possible to analyse in detail the different events involved in the induction of lipolysis by catecholamines It could thus be demonstrated that the lipolytic response to noradrenaline was markedly reduced in specimens from hypothyroid subjects even at high concentrations of the amine (Paper II) while isopropylnoradrenaline theophylline and dibutyryl cyclic AMP retained their potent lipolytic effects (Papers I II V) This demonstrates that the beta-adrenergic receptor – adenyl cyclase – lipase system was not deranged in the hypothyroid state. Furthermore it follows that a decreased availability of the precursor ATP (43) for the conversion to cyclic AMP could not be the underlying mechanism for the reduced noradrenaline response since this would also have reduced the response to isopropylnoradrenaline and theophylline Noradrenaline is a combined alpha and beta adrenergic agonist in human adipose tissue while isopropylnoradrenaline is an almost pure beta-adrenergic agonist (96) The studies of Efendić (23) and Burns and Langley (12) have shown that in human adipose tissue the lipolytic response to beta-adrenergic stimulation can be suppressed by alpha-adrenergic stimulation The beta-adrenergic recep-

tor — adenyl cyclase — lipase system could be readily activated by isopropylnoradrenaline di butyryl cyclic AMP and theophylline Thus the decreased noradrenaline response in adipose tissue from hypothyroid subjects could be due to enhancement of the alpha-adrenergic response

That this indeed was the case was demonstrated by the normalization of the lipolytic response to noradrenaline when the alpha recept ors were blocked with phentolamine (Papers I II) Phentolamine alone did not significant ly influence lipolysis (Paper II) Another possible explanation for the decreased noradrenaline response could have been an enhanc ed uptake of noradrenaline by the nerve endings of the tissues from hypothyroid subjects which would ha left less noradrenaline a ail able for the receptor sites (49) Phentolamine known to inhibit this uptake might then indirect ly ha e stimulated the receptor response to noradrenaline It is then noteworthy that, although the highest concentration of phentol amine used (50 μg/ml) could have exerted such an inhibitory action on the uptake of catechol amines (20 49) the lipolytic effect of noradrenaline still was markedly stimulated by 10 to 100 times lower concentrations of the antag onist (Paper II) *The ffect of phentolamine on* the above uptake mechanisms would be negli *gible at these low concentrations* (49) Furthermore the finding that noradrenaline in the presence of a beta-adrenergic antagonist, propranolol actually stimulated the alpha-adrenergic receptor in adipose tissue from both euthyroid and hypothyroid subjects does also indicate that noradrenaline was not taken up by the nerve endings (Paper III)

The present studies demonstrated that longterm replacement therapy readily restored the lipolytic action of noradrenline (Paper II) In orde to test the a c u t e effect of thyroid hormones T_3 was added to isolated adipocytes from hypothyroid subjects when incubated with catecholamines (Paper IV) No stimulatory effect of T_3 on the action of noradrenaline on the adenyl-cyclase activity was observed. This lack of effect could be due to the fact that the cells were not preincubated with T_3 Preincubation was omitted in our experiments since such a procedure might have changed the rate of ATP synthesis thereby altering the specific activity of the ATP pool. This would have invalidated the adenyl-cyclase assay (see Methods p 14) The concentration of T_3 was the one used by Challoner and Allen (16) who could demonstrate enhancement of the action of adrenaline on cyclic AMP formation after 30 min of preincubation of isolated fat cells from normal rats Our results do indicate however that T_3 has no immediate phentolamine-like effect on the alpha-adrenergic receptors

It is known that the adrenergic response to catecholamines can be modulated by prostaglandin F_1 (41) The addition of PGE_1 to adipose tissue from hypothyroid subjects partly restored the lipolytic response of noradrenaline while the response to isopropylnoradrenaline was inhibited (Paper V) The mechanism behind this *modulatory effect of* PGE_1 *on the noradrenaline* response in tissues from hypothyroid subjects remains unclarified at the moment. It is of interest however that PGE_1 has been demonstrated to modify several processes p obably located at the cellular membranes (14 32 74 76)

The mechanism by which alpha-adrenergic stimulation modifies lipolysis was further investigated in order to elucidate the derangement of the response to noradrenaline induced by the hypothyroid state

Studies on human adipose tissue (79), frog skin preparations (1) isolated pancreatic

islets (85) toad bladders (36) and platelets (73) have given results that are compatible with the hypothesis that alpha-adrenergic stimulation lowers the intracellular level of cyclic AMP (78) The mechanism by which such stimulation exerts its effect is however not clear (37) Two different hypothesis can be envisaged:

inhibition of the formation of cyclic AMP either by direct interaction with the adenyl cyclase enzyme or indirectly by changing some factors e g. the ionic environment of the enzyme

activation of the phosphodiesterase enzyme which converts cyclic AMP to the inactive compound 5 AMP

In the present study noradrenaline in the presence of propranolol diminished basal as well as theophylline-induced lipolysis while that of dibutyryl cyclic AMP was unaffected (Paper III) The direct measurements of adenyl cyclase activity (Paper V) were performed in the presence of 10 $^{-3}$ M theophylline which inhibits the phosphodiesterase enzyme of the cells (12) In spite of this the alpha-adrenergic influence on cyclic AMP formation could readily be demonstrated (Paper V; Figs 1 2) In addition no qualitative differences could be found in the effect of alpha-adrenergic stimulation on cyclic AMP formation, whether phosphodiesterase was blocked or not (Fig 2) All these results are compatible with the idea that alpha adrenergic stimulation lowers the level of cyclic AMP in adipose tissue (Paper III) by inhibiting the adenyl-cyclase activity

In agreement with this it was demonstrated that the enhanced alpha-adrenergic response of adipose tissue in hypothyroidism was accompanied by complete suppression of noradrenaline-stimulated formation of cyclic AMP (Paper V)

Krishna et al (54) using adipose tissue homogenates from hypothyroid rats also demonstrated decreased adenyl-cyclase activity to noradrenaline However they did not test the possibility of increased alpha-adrenergic response in this tissue and therefore their data do not permit discrimination between decreased amounts of enzyme and enhanced alpha-adrenergic response It must also be remembered that the studies of Bray (11) Burns and Langley (12) and Himms Hagen (42) have shown that the alpha-adrenergic response is difficult to demonstrate in adipose tissue from rats Hence it cannot be excluded that the effect of hypothyroidism in the rat is qualitatively different from that in human adipose tissue

How does alpha receptor activation modulate adenyl-cyclase activity in adipose tissue and what step is influenced by the level of thyroid hormones?

The results of the studies on aortic tissue from hypothyroid and control rabbits showed that their ED_{50} values for adrenaline did not differ indicating that the affinity of the alpha-adrenergic receptors to adrenaline (5) probably was unchanged in hypothyroidism On the other hand the contractile response was enhanced in the hypothyroid state demonstrating an augmented effect of the activation of the alpha-adrenergic receptor system Although the same parameters could not be analysed in human adipose tissue the situation here may be analogous to that in the aortic tissue (Paper III)

This difference in contractile response to adrenaline remained unchanged in the presence of lanthanum (La^{+++}) (Paper VI) This ion has a high affinity for the calcium binding sites and displaces calcium ions bound to the outer surface of the cell membrane (87) The use of La^{+++} therefore inhibits the entry of Ca^{++} into the cells and permits the differentia

tion of a contractile response induced by Ca^{++} ions entering smooth muscle cells from that caused by Ca^{++} released from intracellular sites (66) From the present results (Paper VI) it can therefore be assumed that the enhanced alpha response of the aortic strips from hypothyroid animals was not due to an increased uptake of Ca^{++} from the extracellular space since the difference in response remained in the presence of La^{+++}

As to contractile responses due to increased concentrations of intracellular Ca^{++} the findings of an imparied Ca^{++} transport in striated muscles (26) as well as heart muscles (83) of hypothyroid rats are of special interest. Al though the Ca^{++} transporting system of smooth muscle is not completely understood (69) it may be suggested that smooth muscle from hypothyroid rabbits also could have an impaired capacity to transport Ca^{++} out of the cell This would probably lead to increased intracellular concentration of Ca^{++} on alpha-adrenergic stimulation which, in turn might explain the enhanced contractile respons to adrenaline

Ionic changes of the type described above in smooth muscle may also play a role in the lpha-adrenergic control *of the adenyl-cyclase* activation of adipose tissue. Thus Perry and *Hales (75) demonstrated* that alpha-adrenergic response in rat adipose tissue was accompanied by a rapid fflux of K^+ This would probably be accompanied by a concomitant influx of Na and perhaps also by other cations like Ca^{++} and H^+ Since stimulation of adenyl cyclase is known to be enhanced by K^+ and inhibited by Na^+ and Ca^{++} (9 80) such a new ionic environment would produce a less fa ourable condition for the enzyme. Ouabain r a potassium-free medium which increase the intracellular content of sodium diminished catecholamine-induced lipolysis (57) This would also be compatible with the above assumption. On the other hand, the short time incubation studies presented here demonstrated an alpha response already after 15 sec (Fig 2) and it is unlikely that the necessary ionic shifts could have been established that rapidly

It cannot be excluded, however that alpha-adrenergic stimulation is accompanied by a rapid influx of sodium into the cells which leads to release of Ca^{++} from cellular stores This might, in turn, affect the adenyl-cyclase activ ity Such an interrelationship has been suggest ed for the exitation-contraction coupling in heart muscle (59)

The ionic composition of cells also seems to be influenced by the level of thyroid hormones Thus Ismail Biegi and Edelman (47) and Claret and Coraboeuf (17) demonstrated increased intracellular concentrations of sodium in tissues from hypothyroid animals This was most probably the result of a deficient NaK ATPase system in the cells (46) Reduction of heart muscle NaK ATPase by digitalis led to increased intracellular concentrations of Na^+ which, in turn facilitated the entry of Ca^{++} into the cytoplasm (60) In the same way a decreased NaK ATPase activity in hypothy*roidism ould* be accompanied by an increased intracellular availability of Ca^{++} This might result in an enhanced concentration of calcium ions in the cells on alpha-adrenergic stimulation. In the case of the aortic tissue this relationship is obvious since the muscular contraction is initiated by Ca^{++} Furthermore the finding (Paper VI) that more Ca^{++} remained in the aortic tissue from the hypothyroid rabbits than from the controls after incubation in Tris-La^{+++} would fit this assumption. As to adipose tissue the effect of alpha-adrenergic stimula tion may normally be mediated by ionic shifts (75) including shift of Ca^{++} (ee above) Hence

an increased availability of Ca^{++} due to a deficient NaK-ATPase could explain the present findings of an enhanced alpha-adrenergic response in adipose tissue from hypothyroid subjects

If this interpretation is the correct one it would imply that the alpha-adrenergic receptors per se are not modified by the hypothyroid state but that the biological response evoked by stimulation of these receptors is amplified due to changes in the ionic "milieu intéreur'

In conclusion the studies on the relationship between thyroid hormones and catecholamines have shown that the hypothyroid state is accompanied by an enhanced alpha adrenergic response in at least two kinds of tissues In adipose tissue it was found that the alpha receptor inhibits the adenyl-cyclase activity thereby inhibiting lipolysis In smooth muscle the enhanced response resulted in increased contractile strength. The mechanisms by which hypothyroidism alters the responsiveness of alpha receptors remain obscure but some evidence suggests that decreased NaK ATPase activity and the ensuing shift in intracellular ion composition may form the basis for the enhanced alpha-adrenergic response.

SUMMARY

It was demonstrated that the alpha-adrenergic responsiveness was enhanced in subcutaneous adipose tissue from hypothyroid subjects while the beta-adrenergic response was not changed. This resulted in a complete suppression of the lipolytic response to noradrenaline in this tissue Isopropylnoradrenaline theophylline and dibutyryl cyclic AMP were on the othe hand, potent stimulators of lipolysis in adipose tissue from hypothyroid subjects The deranged adrenergic response ould be partly normalized with PGE_1 but not by the immediate action of T_3 in vitro Replacement therapy with thyroid hormones restored the lipolytic activity of noradrenaline by diminishing the alpha receptor responsiveness

The alpha-adrenergic response in adipose tissue from normal and hypothyroid subjects was found to reduce the level of cyclic AMP through inhibition of the adenyl-cyclase enzyme In adipose tissue from hypothyroid subjects the alpha receptor response to noradrenaline was so prominent that no stimulation of the f rmation of cyclic AMP occurred with amine

A similar enhancement of alpha-adrenergic response was als demonstrated in aortic strips from hypothyroid rabbits while the response to histamine and K were unchanged.

It is concluded that the hypothyroid state modifies the response to noradrenaline in some tissues by enhancing alpha-adrenergic receptor function. Furthermore it is proposed that the enhanced alpha-adrenergic response may be due to a diminshed NaK ATPase activity

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REFERENCES

1 Abe K Robison G A Liddle G W Butcher R W Nicholson W E & Baird, C E Role of cyclic AMP in mediating the effects of MSH norepinephrine and melatonin on frog skin color Endocrinology 85 674 1969

2. Ahlquist, R P A study of the adrenotropic receptors Amer J Physiol 153 586 1948

3 Angel A Desai K S & Halperin M L. Reduction in adipocyte ATP by lipolytic agents relation to intracellular free fatty accumulation. J Lipid Res 12 203 1971

4 Anton, A H. & Gra enstein, J S Studies on thyroid-catecholamine interactions in the isolated rabbit heart. Europ J Pharmacol 10 311 1970

5 Ariëns E.J Simonis A M & Van Rossum J M Drug receptor interaction interaction of one or more drugs with one receptor system In Molecular Pharmacology (ed. E J Ariëns) vol I p 119 Academic Press New York 1964

6 Arner P & Östman, J Determination of mono- and diglyc rides in human adipose tissue Submitted for publication to J Lipid Res

7 Aumann K W & Youmans W B. Differential sensitization of adrenergic neuroeffector systems by thyroid hormone Am r J Physiol 131 394 1940

8 Bauer H Goodford P J & Hüter J The calcium content and ^{45}calcium uptake of the smooth muscl of the guinea-pig taenia coli J Physi l (Lond.) 176 163 1965

9 Birnbauer L Pohl S.L. & Rodbell M Adenyl cyclase in fat cells 1 Properties and the effects of adrenocorticotropin and fluoride. J biol Chem 244 3468 1969

10 Björntorp P & Östman J Human adipose tissue Dynamics and regulation. In Advances in metabolic dis rders (eds R Levine & R Luft) ol 5 p 277 Academic Press New York and London 1971

11 Bray G A Studies on the sensitivity to catecholamines after thyroidectomy Endoc inology 79 554 1966

12 Burns T W & Langley P E Lipolysis by human adipose tissue the role of cyclic 3 5 -adenosine monophosphate and adrenergic receptor sites J Lab clin. Med. 75 983, 1970

13. Butcher R.W & Sutherland, E.W : Adenosine 3 5 -phosphate in biological materials I. Purification and properties of cyclic 3 5 nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3 5 -phosphate in human urine J biol. Chem 237: 1244 1962

14 Böhle E Döbert E. Ammon J & Ditschuneit, H. Über Stoffwechselwirkungen von Prostaglandinen. I. Der Einfluss on Protaglandin E_1 auf den Glucose- und Fettstoffwechsel des epididymalen Fettgewebes der Ratte Diabetologia 2 162 1966

15 Caircli, V & Crout J R Role of the autonomic nervous system in the resting tachycardia of experimental hyperthyroidism. J Pharmacol exp Ther 158 55 1967

16 *Challoner D R & Allen D O An in* vitro effect of triiodothyronine on lipolysis, cyclic AMP-C^{14} accumulation and oxygen consumption in isolated fat cells Metabolism 19 480 1970

17 Claret, M. & Coraboeuf E. Effets des hormones thyroïdiennes et surrénaliennes sur les potenti ls cellulaires et les concentrations ioniques de foie de rat. C.R. Soc Biol. (Paris) 162 1100 1968

18 Cohen, P P Suspending media for animal tissues In Manometric techniq es (eds W W Umbreit, R H Burris & J F Stauffe) p 147 Burgess Publ C Minneapolis 1957

19 Debons A F & Schwartz I.L. Dependence of the lipolytic action of epinephrine in vitro upon thyroid hormone. J Lipid Res 2 86 1961

20 Dengler H J Spiegel H E & Titus E O Effects of drugs on uptake of isotopic norepinephrine by cat tissue Nature (Lond) 191 816 1961

21 Discala, V A & Kinney M J Effects of myxedema on the renal diluting and concentrating mechanism Amer J Med. 50 325 1971

22 Dousa, T & Rychlik, I : The metabolism of adenosine 3 5 –cyclic phosphate. I Method for the determination of adenyl cyclase and some properties of the adenyl cyclase isolated from the rat kidney Biochim biophys Acta (Amst.) 204.1 1970

23 Efendić S. Studies on the effect of catecholamines on human adipose tissue metabolism Thesis Stockholm 1970

24 Efendić S Influence of prostaglandin E_1 on lipolysis induced by noradrenaline isopropylnoradrenaline, theophylline and dibutyryl cAMP in human omental adipose tissue in vitro Acta med. scand. 187 503 1970

25 *Eppinger H Falta, W & Rudinger C.* Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion. Z. klin Med. 66 1 1908

26 Fanburg B.L Calcium transport by skeletal muscle sarcoplasmic reticulum in the hypothyroid rat. J clin Invest. 47 2499 1968

27 Furchgott, R F : Dibenamine blockade in strips of rabbit aorta and its use in differentiating receptors J Pharmacol exp Ther 111 265 1954

28 Gale C C Williams R. & Toi ola P Thyroid-sympathetic nervous system interactions in thermoregulation. Acta endocr (Kbh.) Suppl. 155 34 1971

29 Gleason, M N Gosselin, R E & Hodge H C Clinical toxicology of commercial products Acute poisoning, p 137 Williams & Wilkins Baltimore 1963

30 Goetsch, E New methods in the diagnosis of thyroid disorders pathological and clinical N Y St. J Med. 18 259 1918

31 Goodman, H.M & Knobil E : Mobilization of fatty acids by epinephrine in normal and hypophysectomized rhesus monkeys Proc Soc exp Biol (N Y) 100 195 1959

32 Grantham J J & Orloff J Effect of prostaglandin E_1 on the permeability response of the isolated collecting tubule to vasopressin, adenosine 3 5 monophosphate and theophylline J clin. Invest. 47 1154 1968

33 Grill V & Rosenqvist, U manuscript in preparation.

34 Hallert, B Elementär felteori för mätningar P A Norstedt & Söner Stockholm 1967

35 Hamburger J Smith, R W Jr & Miller J M. : Effects of epinephrine on free fatty acid mobilization in hyperthyroid and hypothyroid subjects Metabolism 12 821 1963

36 Handler J Bensinger R & Orloff J Effect of adrenergic agents on toad bladder response to ADH 3 5 AMP and theophylline Amer J Physiol 215 1024 1968

37 Hardman J G Robison, G A and Sutherland, E W Cyclic nucleotide Ann. Rev Physiol. 33: 311 1971

38 Harlan, W R Laszlo J Bogdonoff M D & Estes E H : Alterations in free fatty acid metabolism in endocrine disorders Part I: Effect of thyroid hormone J clin Endocr 23 33 1963

39 Harrison T S Reflex liberation of *catechol hormones in hyperthyroidism* J surg Res 1 77 1961

40 Harrison, T S : Adrenal medullary and thyroid relationships Physiol Rev 44; 161 1964

41 Hedqvist, P Studies on the effect of prostaglandin E_1 and E_2 on the sympathetic neuromuscular transmission in some animal tissue Acta physiol scand. Suppl 345 1970

42 Himms-Hagen J Adrenergic receptors for metabolic responses in adipose tissue Fed. Proc 29: 1388 1970

43 Hoch F L Biochemistry of hyperthyroidism and hypothyroidism Postgrad med J 44 347 1968

44 Häggendal J Some further aspects on the release of the adrenergic transmitter In: New aspects of storage and release mechanisms of catecholamines Bayer Symposium II (eds H J Schümann & G Kroneberg) p 100 Springer Verlag Berlin Heidelberg New York 1970

45 Hökfelt, B. Noradrenaline and adrenaline in mammalian tissue Distribution under normal and pathological conditions with special reference to the endocrine system Acta physiol scand 25 Suppl 92 1951

46 Ishida, N Metabolism of catecholamines in hyper- and hypo-thyroid patients J exp Med. 78 228 1962

47 Ismail Beigi F & Edelman I S Mechanism of thyroid calorigenesis role of active sodium transport Proc nat Acad Sci (Wash) 67 1071 1970

48 Ismail Beigi F & Edelman, I S The mechanism of the calorigenic action of thyroid hormone Stimulation of Na^+ K -activated adenosinetriphosphatase activity J gen Physiol 57 710 1971

49 Iversen, L L : The uptake and storage of noradrenaline in sympathetic nerves Cambridge Univeristy Press 1967

50 Johnson G E Flattery K V & Schönbaum E : The influence of methimazole on the catecholamine excretion of cold-stressed rats Canad. J Physiol Pharmacol 45 415 1967

51 Kolthoff I M & Sandell E B : Text book of quantitative inorganic chemistry ed. 3 p 631 Macmillan Co New York 1959

52 Koschinsky T & Gries F A : Glycerin-Kinase und Lipolyse des menschlichen *Fettgewebes in Abhängigkeit om relati* ven Körpergewicht. Hoppe-Seylers Z physiol Chem 352: 430 1971

53 Krishna G & Birnbaumer L On the assay of adenyl cyclase Analyt. Biochem 35 393 1970

54 Krishna, G Hynie S & Brodie B. B. Effects of thyroid hormones on adenyl cyclase in adipose tissue and on free fatty acid mobilization Proc nat. Acad Sci (Wash.) 59 884 1968

55 Kuo, J F & De Renzo, E C A comparison of the effects of lipolytic and antilipolytic agents on adenosine 3 5 -monophosphate levels in adipose cells as determined by prior labeling with adenine-8-^{14}C J biol. Chem 244 2252, 1969

56 Kusonke H J Wernze H & Becker G Sympatho-adrenal acti ity in thyrotoxicosis Brit. med J 1 1656 1960

57 Kypson J Triner L & Nahas G G Effects of ouagain and K free medium on acti ated lipolysis and epinephrine-stimulated glycogenolysis J Pharma c exp Ther 159 8 1968

58 Landsberg L & Axelrod, J Influence *of pituitary thyroid and adrenal hor-* mones on n repinephrine turnover and metabolism in the rat heart. Circulat. Res 22 559 1968

59 Langer G A The intrinsic control of myocardial contraction — ionic factors New Engl J Med 285 1065 1971

60 Langer G A & Serena, S D Effects of strophanthidin upon contraction and ionic exchange in rabbit ventricular myocardium relation to control of active state J molec cell Cardiol 1 65 1970

61 Larsen, J A Elimination of glycerol as a measure of the hepatic blood flow in the cat Acta physi l scand 57 224 1963

62 Laurell, S & Tibbling, G The use of blood glycerol determination in the diagnosis of hyperthyroidism Clin chim Acta 21 127 1968

63 Leak, D The thyroid and the autonomic nervous system William Heinemann Medical Books Ltd, London 1970

64 Leak D Brunjes S Johns V J & Starr P Adrenal medullary response to insulin hypoglycemia in hypothyroid patients J Lab clin Med 60 811 1962

65 Lee T P Kuo, J F & Greengard P Regulation of myocardial cyclic AMP by isoproterenol glucagon and acetyl choline Biochem biophys Res Commun. 45 991 1971

66 Levey G S Catecholamine sensitivity *thyroid hormone* and the heart. *Amer* J Med 50 413 1971

67 Levine R J Oates J A Vendsalu A & Sjoerdsma, A : Studies on the metabolism of aromatic amines in rela tion to altered thyroid function in man J clin Endocr 22 1242 1962

68 Lutherer L O Fregly M J & Anton, A H An interrelationship between theophylline and catecholamines in the hypothyroid rat acutely exposed to cold. Fed Proc 28 1238 1969

69 Lüllamnn H : Calcium fluxes and calcium *distribution in smooth muscle In Smooth* muscle (eds E Bülbring A Brading A Jones & T Tomita) p 151 Edward Arnold Ltd London 1970

70 Macmillan, W H & Rand, M J The effects in rabbits of thyroidectomy and treatment with triiodothyronine on the sensitivity to noradrenaline and the content of noradrenaline in aorta and spleen J Pharm Pharmacol 14 257 1962

71 Mandel L R & K ehl F A Jr Lipolytic action of 3, 3 5-triiodo-l thyronine, a cyclic AMP phosphodiesterase inhibi tor Biochem biophys Res Commun. 28 13, 1967

72 Margolius H S & Gaffney T E The effects of injected norepinephrine and sympathetic nerve stimulation in hypothyroid and hyperthyroid dogs J Pharmacol exp Ther 149 329 1965

73 Moskowitz J Harwood J P Reid W D & Krishna, G The interaction of norepinephrine and prostablandin E_1 on the adenyl cyclase system of human and rabbit blood platelets Biochim biophys Acta 230 279 1971

74 Paton D M & Daniel, E E On the contractil response of the isolated rat uterus to prostablandin E_1 Canad. J Physiol Pharmacol 45 795 1967

75 Perry M C & Hales C N Factors affecting the permeability of isolated fat-cells from the rat to ^{42}K potas sium and ^{36}Cl *chloride ions* Biochem J 117 615 1970

76 Piccinini F Pomarelli P & Chiarra A : Further investigations on the mechanism of the inotropic action of prostaglandin E_1 in relation to the ion balance in frog heart Pharmacol Res Commun 1 381 1969

77 Pybus J Determination of calcium and magnesium in serum and urine by atomic absorption spectrophotometry Clin chim Acta 23: 309 1968

78 Robison, G A & Sutherland, E W Sympathin E sympathin I and the intracellular level of cyclic AMP Circulat. Res 26-27 I 147 1970

79 Robison, G A Langley P E & Burns T W Adrenergic receptors in human adipocytes – divergent effects on adenosine 3 5 -monophosphate and lipolysis. Biochem Pharmacol 21 589 1972

80 Rodbell M Brinbaumer L & Pohl S L In The role of adenyl cyclase and cyclic 3 5 -AMP in biological systems p 59 Fogarty international center proceedings no 4 U S Government print ing office Bethesda 1971

81 Shephard, J T Physiology of the circulation in human limbs in health and disease p 366 W B Saunders Co Philadelphia and London 1963

82 Smith U : Experimental studies on human adipose tissue With special reference to cell size Thesis Gothenburg 1970

83 Suko, J Alterations of Ca^{2+} uptake and Ca^{2} -activated ATPase of cardiac sarcoplasmic reticulum in hyper- and hypothy roidism Biochim biophys Acta (Amst) 252 324 1971

84 Surveyor I Sodium potassium and water metabolism in myxoedema. Postgrad. med J 45 659 1969

85 Turtle J R. & Kipnis D M An adrenergic receptor mechanism for the control of cyclic 3 5 adenosine monophosphate synthesis in tissues Biochem biophys Res Commun. 28 797 1967

86 Van Breemen C : Blockade of membrane calcium fluxes by lanthanum in relation to vascular smooth muscle contraction Arch int. Phys Biochim 77 710 1969

87 Van Breemen & Neughton, E : The separation of cell membrane calcium transport from extracellular calcium exchange in vascular smooth muscle Biochem biophys Res Commun. 39: 567 1970

88 Van Rossum J M & Van den Brink, F G : Cumulative dose-response curves II Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters Arch int. Pharmacodyn 143 240 1963

89 Vaughan M : An in vitro effect of tri iodothyronine on rat adipose tissue J clin Invest 46: 1482 1967

90 Waldstein, S S Thyroid – catechol amine interrelations Ann Rev Med 17: 123 1966

91 Wieland O : Eine enzymatische Methode zur Bestimmung von Glycerin Biochem Z 329 313 1957

92 Wiswell J G Hurwitz G E Coronho, V Bing O H L & Child D L Urinary catechol amines and their metabolites in hyperthyroidism and hypothyroidism J clin Endocr 23 1102 1963

93 Wurtman, R J Kopin I J & Axelrod, J Thyroid function and the cardiac dis position of catecholamines Endocrinology 73 63, 1963

94 Zsotér T Tom H & Chappel C Effect of thyroid hormones on vascular response J Lab clin Med 64 433 1964

95 Östman J A procedure for in vitro studies on fatty acid metabolism by human subcutaneous adipose tissue Acta med. scand. 177 183, 1965

96 Östman, J & Efendić S Catecholamines and metabolism of human adipose tissue II Effect of isopropylnoradrenaline and adrenergic blocking agents on lipolysis in human omental adipose tissue in itro. Acta med scand 187 471 1970

97 Östman J & Arner P manuscript in preparation

76 Piccinini F Pomarelli P & Chiarra, A Further investigations on the mechanism of the inotropic action of prostaglandin E_1 in relation to the ion balance in frog heart. Pharmacol Res Commun 1: 381 1969

77 Pybus J Determination of calcium and magnesium in serum and urine by atomic absorption spectrophotometry Clin chim Acta 23 309 1968

78 Robison G A & Sutherland, E W Sympathin E sympathin I, and the intracellular level of cyclic AMP Circulat. Res 26-27: I 147 1970

79 Robison, G A Langley P E & Burns T W : *Adrenergic receptors in* human adipocytes — divergent effects on adenosine 3 5 monophosphate and lipolysis Biochem Pharmacol 21 589 1972

80 Rodbell M Brinbaumer L & Pohl S L In The role of adenyl cyclase and cyclic 3 5 -AMP in biological systems p 59 Fogarty international center proceedings no 4 U S Government printing office Bethesda 1971

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82 Smith, U Experimental studies on human adipose tissue With special reference to cell size Thesis Gothenburg 1970

83 Suko, J Alterations of Ca^2 uptake and Ca^2 -activated ATPase of cardiac sarcoplasmic reticulum in hyper and hypothyroidism Biochim biophys Acta (Amst) 252 324 1971

84 Surveyor L Sodium potassium and water metabolism in myxoedema. Postgrad. med. J 45: 659 1969

85 Turtle J R & Kipnis D M An adrenergic receptor mechanism for the control of cyclic 3 5 adenosine monophosphate synthesis in tissues Biochem biophys Res Commun. 28 797 1967

86 Van Breemen C Blockade of membrane calcium fluxes by lanthanum in relation to vascular smooth muscle contraction Arch int. Phys Biochim 77 710 1969

87 Van Breemen & Neughton E The separation of cell membrane calcium transport from extracellular calcium exchange in vascular smooth muscle Biochem biophys Res Commun. 39: 567 1970

88 Van Rossum J M & Van den Brink, F G Cumulative dose-response curves II Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters Arch int Pharmacodyn 143 240 1963

89 Vaughan, M An in vitro effect of tri iodothyronine on rat adipose tissue J clin. Invest 46: 1482 1967

90 Waldstein, S S Thyroid — catechol amine interrelations Ann Rev Med. 17: 123 1966

91 Wieland O Eine enzymatische Methode zur Bestimmung von Glycerin Biochem Z 329 313 1957

92 Wiswell J G Hurwitz G E Coronho V Bing O H L & Child, D L : Urinary catechol amines and their metabolites in hyperthyroidism and hypothyroidism J clin Endocr 23 1102 1963

93 Wurtman, R J Kopin I J & Axelrod, J Thyroid function and the cardiac dis position of catecholamines Encocrinology 73 63 1963

94 Zsotér T Tom H & Chappel C : Effect of thyroid hormones on vascular response J Lab clin Med 64 433 1964

9 Östman J A procedure for in vitro studies on fatty acid metabolism by human subcutaneous adipose tissue Acta med scand 177 183, 1965

96 Östman, J & Efendić S : Catecholamines and metabolism of human adipose tissue II Effect of isopropylnoradrenaline and adrenergic blocking agents on lipolysis in human omental adipose tissue in vitro Acta med scand 187 471 1970

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POLYMYALGIA ARTERITICA

by Bengt Hamrin

with

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by Görel Östberg

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Polymyalgia Arteritica

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Polymyalgia Arteritica

by

BENGT HAMRIN

with

Morphological Changes in the Large Arteries in Polymyalgia Arteritica

by

GÖREL ÖSTBERG

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CONTENTS

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He also mentioned that in elderly persons isolated, mild peritendinitis may also be associated with elevation of the E. S R., though not so marked as in the 41 cases he had studied He also described the prognosis as worse than in younger persons, a postulation contradicted to some extent by the case reports in his short article He did not mention how long he had followed up his patients, but it was evidently for only a short time.

Cecil and Kammerer (1951) had personally studied 100 consecutive cases of rheumatoid arthritis that had originally appeared in patients above 60 years and seen in the Arthritic Clinic at New York Hospital and in their own private practice. They found that the disease in their series differed in some respects from that commonly seen in persons in whom the affection had appeared earlier in life. In their series

the s x distribution was exactly 1 1

invol ement of shoulde joints was more common,

a high E. S.R was a frequent finding

osteoporosis was often demonstrable roentgenographically and this was complicated also by the fact that osteo-arthritis is common in advanced age

On the other hand, n difference was found in the course or prognosis between younger and older patients. The authors were especially intrigued by the high frequency of shoulder involvement in their series and by the fact that shoulder pain was often the initial symptom "in a considerable number the condition was ushered in by what seemed to be an almost typical shoulder-hand syndrome and certainly would have been diagnosed as such had it not progressed to the involvement of other joints. A shoulder hand syndrome was also the provisional diagnosis in the one and only illustrative case, but that diagnosis was ruled out by the high E.S.R. in that patient.

In view of the deviations reported it is somewhat surprising that Cecil and Kammerer concluded that "rheumatoid arthritis in the aged does not differ in any essential respect from rheumatoid arthritis in the earlier decades of life.

It might be observed that in the investigations referred to some of the observations in rheumatoid arthritis in elderly persons were common to both series, namely the periarticular localisation of the symptoms and involvement of the shoulder joints and the marked effect of the disease on the patients' general condition manifested by among other things, a high E.S.R. Another common feature of these two series (Schnell 1941 and Cecil & Kammerer 1951) was that the diseases were regarded as variants of rheumatoid arthritis.

POLYMYALGIA RHEUMATICA

Though the clinical features of rheumatoid arthritis in aged patients has received little space in less recent literature, a common belief among experienced clinicians is that rheumatoid arthritis appearing late in life runs a different and less serious course than that manifesting itself early From the variety of more or less well defined rheumatic diseases attempts have also been made during the last two decades at European centres to distinguish

syndrome comprising certain features of rheumatoid arthritis and of extra-articular clinical pictures such as periarthritis humeroscapularis and its many synonyms.

This syndrome is at present usually called polymyalgia rheumatica (Barber 1957) but it is also known under many other names (Table 1) Ther

T ble 1 Synonyms of polymyalgia rheumatica.

Authors	The various names used in the literature
Bruce (1888)	Senile rheumatic gout
Meulengracht (1945)	Periarthrosis humeroscapularis with general symptoms
Holst and Johansen (1945)	Peri-extraarticular "rheumatism
Kersley (1951)	A myalgic syndrome of the ged with systemic raction
Porsman (1951)	A special type of arthritis in old age
Forestier and Certonciny (1953)	Pseudo-polyarthrite rhizomélique
Bagratuni (1956)	Anarthritic rheumatoid disease
Barber (1957)	Polymyalgia rheumatica
Serre et al. (1962)	Rhumatisme inflammatoire rhizomélique des gens agés
Oldberg (1942)	Arteritis senilis
Olhagen (1963),	Arteritis senilis
Alestig and Barr (1963)	Arteritis senilis
Hamrin et al. (1964)	Polymyalgia arteritica

appears to be general agreement that the various names used by these authors refer to one and the same disease. The disease occurs mainly in persons *above 50 years. Its onset may be acute or insidious* with constitutional symptoms and signs and rheumatic symptoms, such as symmetric pain, tenderness and pain of the muscles on movement and pain in the periarticular tissue *in the region of the neck, in the shoulders and in the hips. The symptoms in* these regions dominate the clinical picture which is, however, not infrequently accompanied by rheumatic symptoms also in the distal parts of the limbs. *A frequently severe malaise and a high E. S.R. often* give the clinical picture a serious appearance. Most patients apparently recover within 2—3 years, sometimes earlier, while in others the course may *be more prolonged with exacerbations. The condition* can also recur. As for the late prognosis, no unanimity has been achieved.

Copeman (1961) stated that the clinical picture of polymyalgia was wellknown *to the older generation* and that his teacher had taught him that the disease was a variant of rheumatoid arthritis which often occurred in elderly persons and that he therefore referred to the condition as the "senile" type *of rheumatoid arthritis. It was considered to be* benign. This view was also more or less tacitly accepted at Professor Waldenström's clinic in the 1950s, where it had presumably been kept alive *by word of mouth rather than by the literature at* that time when our knowledge in this domain was still very vague. Descriptions of polymyalgia have, however, been traced in older literature. Portman *(1951), for example, referred to an article by the* Scottish physician, Bruce (1888). On the basis of 5 cases he described a disease, which he thought to differ clearly not only from gout and rheumatism [illegible] febris rheumatica, but also from rheumatoid arthritis defined by A. B. G[illegible]rrod (1876) [illegible]nd [illegible]eferred to above. Bruce suggested the name [illegible] he[illegible] m[illegible] [illegible]c gout for his syndrome and pointed [illegible] th[illegible] th[illegible] dise[illegible]se w[illegible]s [illegible]emark[illegible]ble in its severity and [illegible] [illegible] even at [illegible] [illegible]ery advanced time [illegible]f [illegible]

In the [illegible] the dise[illegible]se was first des[illegible]cr[illegible]bed [illegible] [illegible] Meulengracht (1945) thus [illegible] [illegible] dise[illegible]se which he felt had not be[illegible] [illegible] [illegible]bed [illegible]n the lite[illegible]rature. The [illegible] [illegible] [illegible]ear-old professor wh[illegible] [illegible] had had bilateral shoulder [illegible] and had lost bodyweight. The preliminary diagnoses were periarthrosis humeroscapularis, myalgia glutealis, febrility and raised E. S. R. In the course of 3 *months' treatment in hospital* the shoulders became stiff, body temperature persisted around 38 C and the E. S. R. varied between 67 and 100 mm/l hr. He was discharged unimproved. During the following year, by which time he had had the disease for 2 *years, he improved spontaneously, increased in* weight and the E. S. R. fell to 10 mm/l hr. The second case, in which the course was similar, was seen in a 68 year-old woman. She lost 17 kg during her illness. *In the discussion of these interesting* case reports Meulengracht wrote that there are some extreme variants of periarthrosis humeroscapularis characterised by systemic symptoms, fever, raised E. S. R. *and loss of bodyweight. The observa*tions in these cases were novel, but the author stressed that they did not help to explain the origin of periarthrosis humeroscapularis, a disease, whose aetiology and pathogenesis are still enigmatic.

Holst and Johansen (1945) described a special type of "rheumatic" disease. Their paper included 5 case reports, essentially similar to those published by Meulengracht and referred to above. *They also shared Meulengracht's opinion and* assumed "that if greater attention were paid to cases of peri- and extraarticular rheumatism particularly a more frequent examination of tempera*ture and the sedimentation rate of the red blood* corpuscles, it would lead to recognition of numerous cases". They also thought the adjective "rheumatic" to be vague and often to be used in the loose sense of the term *and pointed out that nosography* is very important in the discussion of diseases of unknown aetiology.

In a later paper Meulengracht (1950) took up the question of *generalised symptoms of periarthrosis* humeroscapularis. He thought it remarkable that hardly any previous publications had included descriptions of generalised symptoms of the disease or denied their occurrence. *In a personal 5-year series of 82 in-patients with periarthrosis humero*scapularis as the main or secondary diagnosis the E. S. R. was raised in 65 %, it was above 50 mm/1 h in 9 % and above 100 mm/1 hr in 10 %. *Of the patients, 20* % had fever, which in the typical cases was moderate but obstinate. The patients had been ill for up to 2 years before admission, so that these figures must be regarded as minimum values. Meulengracht cited 3 synonyms for periarthrosis

humeroscapularis. He stated that the babylonic confusion of the nomenclature could only be explained by lack of knowledge about the disease which, according to him, had a uniform and very typical clinical picture The question whether cases with generalised symptoms were extreme variants of the periarthrosis humeroscapularis or examples of a separate disease, could not be answered on the basis of his material but Meulengracht thought that there was a gradual transition between cases with and without generalised symptoms. In a later paper dealing with the course and prognosis of the disease (Meulengracht & Schwartz 1952) the age distribution was described as the same in the 23 % of patients with generalised symptoms as in the remainder possibly with a tendency of the ages to be slightly higher in the former group with constitutional symptoms.

Kersley (1951) reported 13 cases of a myalgic syndrome of the aged which he had seen at two rheumatologic clinics during the previous 2 years. The disease had usually begun acutely with pain and tenderness in the scapular muscles and thighs. Mild swelling of the hands had been observed in 2 and of the knees in 1 but neither had developed typical rheumatoid joint changes (arthritic deformities) Bagratuni (1953) described rheumatoid syndrome occurring in the elderly" on the basis of 7 cases treated between 1941—1952 at Radcliffe Infirmary in Oxford All of the patients had been discharged undiagnosed as cases of pyrexia of unknown origin Bagratuni (1956) later presented a larger series. In that series some of the patients had symptoms and signs that had not been described by previous authors, namely gastrointestinal symptoms, skin nodules, rash and conjunctivitis, slightly enlarged lymph nodes and in one case splenomegaly In contrast with previous series, some patients also had a positive Waaler Rose test, though only in mild titers. Both Kersley (1951) and Bagratuni (1956 and 1963) felt that the syndrome was related to rheumatoid arthritis.

Forestier and Certonciny (1953) described a syndrome which they called pseudo-polyarthrite rhizomélique, and which was characterised by:

predilection for the aged
subacute onset
inflammatory character with systemic effect reflected in raised E. S. R
periarticular localisation of rheumatic symptoms to the shoulders hips and sometimes back and back of the neck,
tendency to remission after a period of progression and
healing without or with only minimal sequelae

The authors regarded the syndrome as essentially periarticular and similar in some respect to what the English called "fibrositis (regarding this term, see Slocumb 1936 and Smythe in Hollander's Arthritis and Allied Conditions, 1969), but definitely denied any relationship with periarthritis humeroscapularis. The denial is noteworthy and exemplifies the uncertainty of classification of some of our commonest diseases on nosologic grounds. In order further to elucidate the difficulties and the subjectivity of classifications of rheumatic diseases, in Table 2 attempts have been made to summarise the main theses in the differential diagnostic discussion, conducted by Forestier and Certonciny (1953) regarding distinction of their syndrome from shoulder hand syndrome and periarthritis humeroscapularis.

Under the name of myalgic syndrome with constitutional effects Barber (1957) published 12 case reports of the disease for which he suggested the name since most widely used viz "polymyalgia rheumatica. Like Forestier and Certonciny he pointed out that the patients complaints often fitted in well with a diagnosis of "fibrositis or "muscular rheumatism. Barber stressed the myalgia and systemic symptoms, and he thought it was of little service to regard polymyalgia syndrome as a variant of rheumatoid arthritis, a disease, which is generally recognised by the swelling and deformities of joints Gordon (1960) gave concise and clear description of the clinical picture and carefully analysed his own series with respect to myalgia, other rheumatic symptoms, systemic symptoms and the course and prognosis of the disease Like several earlier authors, he stressed the extremely rapid and favourable effect of cortisone therapy on the disease Since it will probably become more and more difficult in future to study the natural history of the disease, Gordon's 7 cases in which the patients recovered without cortisone treatment, are of special interest. Those 7 patients had had the disease for years to 4 years and 2 months.

In the series referred to above the selection of the patients had been based apparently exclusively on the examiners clinical experience In this connection comparison of the published series might

Shoulder-hand syndrome	Periarthritis humeroscapularis	Pseudo-polyarthrite rhizomélique
Unilateral, occasionally bilateral	Never simultaneous onset in both shoulders, but symptoms may some times be bilateral. Periods of pain and stiffness overlap less than in pseudo-polyarthrite rhizomélique	Always simultaneous onset in region of shoulders. Periods of pain and stiffness overlap more than in periarthritis humeroscapularis.
No signs of inflammation.	No signs of inflammation.	Pronounced inflammatory condition.
General condition unaffected	Little or no impairment of general condition because of pain and sleeplessness.	Clea impairment of general condition.
No information on E. S. R.	E. S. R. normal.	E. S. R. raised.
Hips not involved.	Hips not involved.	Hips generally invol ed.

Tab.e 2. Summary of diagnostic differences, according to Forestier and Certonciny (1953), between poly myalgia rheumatica (pseudo-polyarthrite rhizomélique), on one hand, and shoulder-hand syndrome and shoulder periarthritis, on the other

not be out of place. It cannot always be gathered from the papers whether the patients had been examined in retrospect or prospectively In Bagratuni's (1953) first report the diagnosis was still not firm when the patients were discharged from hospital. In some of Barber's cases the diagnosis also appears to have been made retrospectively or late n the course of the disease Meulengracht (1950) reported, on one hand, that patients admitted to hospital with symptoms of scapulohumeral peri arthritis were closely observed for signs of systemic symptoms Though the methods of choice of patients evidently varied, the series referred to above and some others (Table 3) were strikingly similar regarding the clinical picture and age distribution Some of the authors regarded the syndrome as a variant of rheumatoid arthritis, others stressed its sim larity with shoulder periarthritis The tendency to concen the constellation of symptoms as an in dependent ase was evident In most of the series swell ng l n tional ound peripheral joint espec t h h nds and knees, was reported in onl portion of cases Such cases were g B ratuni as transitory forms of rheum nd suggested a relationship between t n l myalgia The difficulty in relatin houlder-peri arthritis, to the sh me and the many variants of the nd ome seems to have been due h rmation

about systemic symptoms, such as fever and raised E. S R. in these diseases was scanty and contradictory It is surprising that this still seems to be the case In Steinbrocker's chapter on the painful shoul der in Hollander's textbook Arthritis and Allied Conditions (1969) much space is given to speculations and hypotheses about the aetiology and pathogenesis of these conditions, and local symptoms of these related and possibly identical diseases are described in detail etc while no mention is made of possible signs of systemic disease in these often acute and sometimes extremely acute conditions. Meulengracht's papers are therefore very valuable Schnell's (1941) previously mentioned observation that E. S R in isolated, mild periarthritis in aged patients often persists for a long time between 20—50 mm is also of considerable interest.

Various explanations may be offered for our lack of knowledge of the general symptoms in the painful shoulder syndrome such as the fact that the mild cases are not kept under clinical observation the more severe cases are not admitted to hospital until late in the course, and that painful shoulders have not been systematically investigated in long term studies It appears that the purely nosological studies of polymyalgia rheumatica referred to above are the result of a new way of regarding aetiological ly and pathogenetically obscure pathological conditions difficult to define, and that they do not describe a newly discovered disease This is also supported by the observations and investigations published during the 60s, which suggest that the myalgic symptoms may be manifestations of disseminated arteritis. Porsman (1951) was probably the first to point out the sim larity between the clinical

Authors	N of cases			Age at onset		Highest E. S. R.	
	M	F	M+F	Mean	range	Mean	range
Bruce (1888)	5	0	5	69	60—74	—	—
Holst and Johansen (1945)	0	5	5	57	48—61	76	68—100
Porsman (1951)*	19	10	29	—	>60	—	—
Kersley (1951)	4	9	13	71	64—82	74	36—109
Meulengracht and Schwartz (1952)	5	13	18	—	45—80	80	23—147
Bagratuni (1956)*	4	17	21	—	56—82	100	25—148
Barber (1957)	2	10	12	58	46—68	79	45—110
Forestier and Certonciny (1958)	18	30	48	62	48—81	—	—
Gordon (1960)	10	11	21	68	49—82	70	42—122
Boyle and Beatty (1961)*	8	13	21	61	46—76	—	—
Todd (1961)*	4	16	20	68	61—78	112	75—138
MacGregor (1961)*	1	11	12	70	63—77	72	23—125
Total	80	145	225				
	35.5	64.5	100				

Table 3 Survey of literature on polymyalgia rheumatica. Arterial biopsy has not been done in these series. Asterisks denote the authors who have discussed the relation between the polymyalgic syndrome and temporal arteritis.

picture of the disease that he and others had described and that of temporal arteritis Paulley and Hughes (1960) paper contributed considerably to the increase in interest in the clinical features of temporal arteritis during the last decade

TEMPORAL ARTERITIS

The famous English clinician, Jonathan Hutchinson, is given credit for the first description of temporal arteritis. It was published in 1890 in Archives of Surgery Since Hutchinson's description of the local symptoms of temporal arteritis is probably still the best on record, an excerpt of it is given below:

The subject of this case was an old man — — — and he had, I believe, suffered from gout. I was asked to see him because, as I was told, he had "red streaks on his head" which were painful and prevented his wearing his hat. — — — The "red streaks" proved, on examination, to be his temporal arteries, which on both sides were found to be inflamed and swollen. The streaks extended from the temporal region almost to the middle of the scalp, and several branches of each artery could be distinctly traced. The conditions were nearly symmetrical. During the first week that he was under my observation pulsation could be feebly detected in the affected vessels, but it finally ceased the redness then subsided, and the vessels were left impervious cords. — — — W appear to have in this case an unquestionable example of an arteritis which spread along the affected vessels, causing swelling of their external coats and adjacent cellular tissue with congestion of the overlying skin, and which resulted very quickly in occlusion of the vessels It is not proved that there was any thrombosis; it is, indeed, certain that in the first stage there was not.

It was not until 40 years later that the next case of temporal arteritis was published, and then in a paper on intracranial aneurysms (Schmidt 1930) The case had been observed by Erik Warburg in Copenhagen Local symptoms of the temporal arteries had been preceded by prolonged fever with "violent myalgia. After the patient had had temporal arteritis for some months he complained of a sound as if he had one-cylinder motor in his head" and Warburg reported that he had heard a soft noise, synchronous with the pulse, when he placed his ear to the patient s ear on either side. The murmur was thought to be caused by an aneurysm, but since the patient was not examined angiographically the intracranial murmur might perhaps have been due to a postarteritic stenosis as in two patients in Palm s series of temporal arteritis (1958). Also in those two cases the intracranial murmurs had been thought to be due to an aneurysm.

Neither in Hutchinson's nor in Warburg s cases was any biopsy specimen obtained of the temporal artery Biopsy was, however done in 5 of the 7 cases t the Mayo clinic (Horton et al. 193 and 1934 Horton & Magath 1937), evidently without knowledge of the cases referred to above. The

tients ages ranged from 55 to 75 years, and 4 of them were women. The disease was characterised by arteritis of the temporal vessels "with painful tender areas over the scalp and accompanied by headache, general malaise and lassitude, weakness, fever, night sweats, anorexia, loss of weight, anaemia and mild leucocytosis." The temporal artery was sometimes tender along a length of 1—2 cm, but not tender on either side of this length. The authors described nodular swellings along the temporal artery and smaller nodules along small branches in the scalp. In some cases pulsations disappeared in the arteries, in others the pulse became weaker. The duration of the disease was given as 4—6 months. One patient developed diplopia and two had changes in the ocular fundi in the form of "phlebitis" with exudative haemorrhage. In one patient one of the branches of the radial artery was demonstrably involved. Histologically the changes were identical. They consisted of periarteritis and arteritis with circumscribed areas of granulation tissue, which contained multinucleated giant cells. The large number of these cells was stressed as characteristic of the microscopic picture.

Without reference to Horton's publications on temporal arteritis, single clinically observed cases of undoubtedly the same disease have been described (Paviot et al. 1934, Barnard 1935 and Lucien et al. 1939). But, as is the rule in later reports, Jennings (1938) in his publication of the first 2 cases in England in modern times referred to Horton's work. Both cases are described in detail, and especially the first may be said to have anticipated the further development because it illustrates several clinical features of giant-cell arteritis not noticed by others until later. The first case was seen in a 66-year-old woman who became blind on one side, and it is the first time that amaurosis was clearly conceived as an inconstant symptom of temporal arteritis. The description of the protracted course is also well compatible with a severe case of polymyalgia rheumatica. Anisosphygmia with a systolic pressure 35 mm lower in the left arm than in the right was concei ed [illegible] gn of in olvement of large arteries just as an abnormal urinary sediment was thought to be a sign of [illegible] enal [illegible] rteritis. Temporal arteritis was thus already [illegible] onceived by clinicians as generalised arteritis.

Following Jennings [illegible] et (1938) Bam (1938) reported a typical [illegible] of temporal arteritis in which the patient, even [illegible] tter [illegible] ssion of the temporal arteritis, "suffered from muscular rheumatism".

Also the first patient with temporal arteritis reported in Sweden (Oldberg 1942) had symptoms of polymyalgia. The "rheumatic" nature of temporal arteritis was apparently not described in detail before 1944 when Sjövall and Winblad published 2 personal, histologically verified cases. They stated, and rightly so, that until that time 20 cases of temporal arteritis had been published but, that those 20 cases had been observed for only a short time and that it could not be gathered from the publications whether the patients had been symptomfree at the end of the observation period. They had followed their two cases for 8 months and 18 months, respectively. Local symptoms from the temporal arteries occurred during fairly short episodes in a protracted disease whose symptoms closely resemble those of polymyalgia. The patients had not recovered by the end of the observation period. According to the description of the rheumatic symptoms in a later phase of the disease, they appear to resemble the clinical picture of the so-called shoulder-hand syndrome, described some years later by Steinbrocker (1947) and still receiving much space in the literature, especially in the American literature. Sjövall and Winblad (1944) concluded that

as far as the symptoms from the joints play a conspicuous role we tend from a clinical point of view to regard the disease as a form of rheumatic infection, the special type of which may be due to its appearance at such a late age.

During the following years the annual number of case reports of temporal arteritis increased. Andersen (1947) traced 56 cases in the literature, to which he added one of his own. He stressed the systemic nature of the vascular disease and claimed that the local symptoms of the temporal arteries

must be looked upon as a rather insignificant, easily recognisable manifestation of the universal disorder.

Andersen also assumed that some cases may exist without involvement of the temporal arteries or at any rate without clinical symptoms of such involvement, and the same year (1947) he reported that he had observed a case with extremely mild symptoms in the area of the temporal arteries. In 1954 Roux published and analysed 248 cases of temporal arteritis from the literature.

OCULAR SYMPTOMS IN TEMPORAL ARTERITIS

The ocular symptoms were soon conceived as the most serious complications of temporal arteritis. They occur in two forms, namely as ophthalmoplegia and impairment of vision Paresis of the eye muscles sometimes occurs alone in the form of ptosis or diplopia and sometimes together with visual failure and then usually before impairment of vision The ophthalmoplegic symptoms are benign and regress within days or weeks. Impairment of vision is often abrupt and the patient can then describe how a dark shadow so to say appeared in his field of vision

Blindness sometimes occurs during sleep and sometimes slowly and stepwise. Also episodic blind ness, amaurosis fugax, with more or less complete regression may occur Often the blindness is bilateral. In 14 blind patients not treated with steroids (Palm 1958) the second eye had been attacked 0—25 days after the first, and in another series (Russell 1959) between 1—28 days.

After Jennings (1938) report of a case of temporal arteritis with amaurosis similar observations were reported by others (Dick & Freeman 1940, Scott & Maxwell 1941 Johnsson et al. 1943). In a compilation of 57 literature cases of temporal arteritis (Andersen 1947) 5 patients had become blind bilaterally 5 unilaterally 1 had only light perception on the worse eye and 3 had scotoma. In 7 cases diplopia and ptosis had been described. In the large series from the Mayo clinic (Birkhead et al 1957) unilateral or bilateral blindness had occurred in 15 (28 %) of 53 cases before the introduction of steroid therapy and in 13 (24 %) of 55 after the introduction of cortisone therapy The prophylactic effect of steroid therapy on temporal arteritis was generally realised as soon as the substance had become commercially available. As for the prophylactic effect of large doses of steroids on ocular complications, ophthalmologists opinions appear not to differ Birkhead et al. (1957) compared 55 histologically verified cases of temporal arteritis treated with steroids and 53 cases seen before the introduction of steroid therapy regarding the number of patients and the number of eyes with decreased vision on admission and on discharge of the patients from hospital. I the group treated with steroids the number (5 patients) with bilateral blindness at the time of discharge was the same as on admission, while of the group not treated with steroids, 9 patients were blind on both sides on discharge from hospital, compared with 3 on admission The number of blind eyes increased in the steroid group from 16 to 18 (11 %), while in the group not treated with steroids it increased from 16 to 24 (50 %) Similar figures have been published by Palm (1958), who had studied 31 cases of temporal arteritis with impairment of vision. Of these 21 had severe impairment of vision (finger counting or less) bilaterally and 9 unilaterally while 1 patient had a defective field of vision with good central vision In 24 cases with primary involvement of one eye the second eye could serve as a control. In 8 of these cases adequate steroid therapy was given and the second eye was attacked in only one case (13 %), compared with 14 (88 %) of 16 who did not receive such therapy Of 23 patients with normal vision in Russell' series (1959), 10 were treated with steroids and 13 with salicylic preparations. None in the former group developed visual failure, compared with 5 in the latter

In Palm s (1958) investigation of ocular crises in temporal arteritis much importance is attached to the systematic symptoms during the prodromal stage, and it is stressed that the disease during this insidious phase produced no temporal or other typical symptoms In his series a clinically unambiguous diagnosis of temporal arteritis had thus been made in only 8 of the 31 cases, in 12 it was less certain or misunderstood and in 11 there were no records of it In contrast, Russell (1959) claimed that ophthalmic arteritis fortunately almost always is preceded by the characteristic syndrome of temporal arteritis. The differences between these opinions may be ascribed to the fact that all the patients in Palm's material emanated from eye clinics and all had eye symptoms (visual disturbances) while Russell' series was collected at a neurological department and headache was the dominating diagnostic symptom, and less than half of the patients had impairment of vision Palm, and recently also Cullen (1967), stressed that it should be borne in mind that asymptomatic or occult temporal arteritis is a common cause of blindness in elderly persons.

GIANT-CELL ARTERITIS

Sproul and H wthorne (1937) described post-mortem findings in a non-syphilitic, chronic, diffuse mesaortitis in 2 men who had died after prostatectomy and myocardial infarction, respectively The

authors did not feel that the findings were compatible with any known form of aortitis. Similar changes have been described by Gilmour (1941) in the aorta and large arteries at autopsy in 4 cases Gilmour found that the inflammatory changes closely resembled those seen in biopsy specimens of vessels in temporal arteritis. The lesions were confined mainly to the media, whence they appear to spread in the adventitia and intima. Because of the presence of multinucleated giant cells in most of the affected vessels he suggested the name giant cell chronic arteritis for this type of arteritis The microscopic appearance varied from artery to artery in the same case, and from one case to another in the same arteries. In the large arteries from the aortic arch the changes were focal, bilateral and symmetric, while in the aorta they were usually more widespread In none of the cases referred to had temporal arteritis been clinically contemplated or considered. Sproul (1942), however reported a further case of giant-cell arteritis in the aorta and large arteries in a patient who had died from cardiac failure in association with clinically clear-cut temporal arteritis There were thus 7 cases with thoroughly described patho-anatomical changes of syphilitic, cryptogenetic arteritis in the aorta arteries Four were men and 3 were women. One of Gilmour's cases was seen in a 23 year the other cases in patients, aged 50—76 years The extent and results of the histological examination of the aorta and large arteries in these 7 cases are given below where the occurrence of giant cells in the inflammatory tissue is given as giant cell arteritis (GCA)

The aorta was examined microscopically and inflammatory changes were found in all 7 cases and in 4 of them the changes were of the type GCA

The pulmonary artery was examined in 3 cases In 1 case the artery showed changes of the type GCA

The common carotid artery and/or external and internal carotid artery was amined in 6 cases Arteritis was seen in 5 in luding 4 of type GCA

The subclavian artery and or the b achiocephalic trunk was examined in 2 case and both showed GCA

Th common iliac artery was amined in 3 cases (all belonged to Sproul's erie All had arteritis including 2 with GCA

Of the visceral vessels the renal artery was studied in 3 the coeliac artery in 2 and the mesenteric arteries in 1 Only in 1 case were arteritic changes found (Sproul 1942) and in that case signs of arteritis were seen in all 3 of the above mentioned arteries

The 23-year-old woman in Gilmour's series had died from a ruptured aneurysm, extending from the right subclavian artery In that case the post mortem examination revealed also considerable stenosis of the carotid arteries and of the left subclavian artery The aneurysm had been diagnosed *intra vitam* and it had been noticed that the pulsation of the left radial artery had been almost imperceptible Autopsy of one of the older cases in Gilmour's series had also revealed severe stenosis of both internal carotid arteries. The clinical information available in Gilmour's cases is scanty It is, however noteworthy that the young woman had had articular rheumatism and that the 3 older patients had had influenza for 3 5 and 26 months, respectively before death and had apparently had no complete remission after the precursory disease One of these patients had some time after the onset of influenza also had symptoms compatible with temporal arteritis as well as a stenotic murmur It is noteworthy that Gilmour who was a pathologist, did not recognise any essential difference between the vascular changes in the 3 elderly patients and those in the young woman The last mentioned case appears to fit in both clinically and pathologically with the criteria for Takayasu's disease or young female arteritis (Ross & McKusick 1953) It is also worth mentioning that Gilmour had suspected that "probably the effects of old aortitis of the type in question have been seen but were regarded as arteriosclerotic or syphilitic. Since Gilmour's publication, giant-cell arteritis and temporal arteritis have usually been used as synonyms. The term cranial arteritis is sometimes still used. It was introduced by Kilbourne and Wolff (1946) who observed that symptoms suggesting involvement also of cranial arteries other than temporal artery a. ophthalmica, a. occipitalis, a. maxillaris and a. lingualis, were clinically involved in their case of temporal arteritis. On the basis of a personal and thoroughly analysed series of temporal arteritis, Cooke et al (1946) gave a survey of the disease from a clinical and pathological point of view and stressed the generalised nature of the arterial disease. Har

rison (1948) ga e a comprehensive review of 75 literature cases of giant-cell or temporal arteritis, mainly from a pathological point of view

Cardell and Hanley (1951) compiled 27 cases of giant-cell arteritis from the literature In 13 of these, including 1 of their own, post-mortem reports were available Frangenheim (1951) described autopsy of 1 case and Rriama (cit. from Heptinstall et al 1954) reported 1 case. Heptinstall et al. (1954) described 11 personal cases of giant-cell arteritis or temporal arteritis including 3 that had been exa mined post mortem. The papers referred to above include post-mortem reports of 18 cases of giant cell arteritis. The arteries with arteritic changes are listed below where the figures in brackets denote the number of vessels involved by the change in question

Aorta (17)

Pulmonary artery (3)

Cervical and cranial arteries. Carotids (14), vertebral arteries (3), basilar artery (1), ophthalmic arterie (2), retinal artery (1), occipital arteries (2).

Arteries in upper limbs. Brachio-cephalic trunk (6), subclavian (8), axillary (2) and radial (1).

Arteries in low limb Iliac (8), femoral (4) popliteal (2).

Visceral arteries Coronary (6), coeliac (4), mesenteric (3), enal (3), hypogastric (2) and ovarian (1).

It is clear from the list that the aorta was almost invariably affected. Since information about the other vessels is incomplete regarding the frequency f the examinations it is not possible to say any thing definite about the extent of the process. The compilation nevertheless suggests that the inflammatory process is confined mainly to the aorta, the large and middle-sized arteries. This is also supported by the thorough post-mortem study in one case by Frangenheim (1951), who found all the changes to be confined to the aorta and the large arteries of the limbs and viscera and their branches, while the small rteries inside the organs were un affected The intensity of the inflammation also tended to decrease centrifugally from the aorta.

POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

It is clear from the preceding sections that rheumatic symptoms, compatible with what was later con sidered characteristic of polymyalgia rheumatica had sometimes been described in temporal arteritis, besides which such cases may be traced in the scanty clinical information on autopsy cases of giant-cell arteritis in the patho-anatomical literature

Porsman (1951) stressed, as mentioned, the many clinical similarities between what he himself called a special type of arthritis in old age and temporal arteritis. Apart from local symptoms in the region of the temporal artery however according to Porsman (1951), the following features are common to temporal arteritis and the form of rheumatic disease, described by him

predilection for advanced age

subacute fever

ery high E. S R.,

symptoms from large joints especially so-called painful shoulder

general malaise and

protracted course of diseas but with good prognosis provided the arteries to ital organs are not affected.

Porsman stressed that several authors had shown that temporal arteritis is a generalised vascular disease, and he therefore questioned whether also this special type of rheumatic symptoms might not be a manifestation of arteritis. Porsman s contribution was mad at the 2nd European Congress of Rheumatology in Barcelona and appears not to have received the attention it deserved. In the 1950s some clinicians presented similar views following the interest aroused by the work of Bagratuni (1953 and 1956). Paulley (1956) reported that he had seen cases similar to those described by Bagratuni, which after a long observation period showed signs of cranial arteritis and, second, cases of cranial ar teritis which after steroid therapy for some time recurred with symptoms fitting in with "Bagratuni arthritis. Kersley (1956) found it "almost im possible to distinguish between Bagratuni's rheumatoid disease and "the prodromal phase of the much more rare cranial arteritis. In an article which received much attention Paulley and Hughes

(1960) presented arguments for the view that giant cell arteritis is a common disease in elderly persons with a variety of frequently misinterpreted symptoms, a fact which they ascribed to the examiners attaching too much importance to the classical symptoms of temporal arteritis. One detail in that paper is noteworthy namely the method for de termining the suspension stability of the erythrocytes. In 5 of their patients the E. S R. was normal (Wintrobe) and in 1 of them the E. S R., as de termined by Westergren s method was 85 mm/1 hr They therefore afterwards used the latter method Westergren s method is now the one generally used, though there are exceptions, such as Boyle and Beatty (1961), in the present reference list.

Polymyalgia rheumatica was discussed in an Editorial in the Lancet (1961) in which it was suggested that the possibility of the pathogenetic role played by the giant-cell arteritis in this syndrome deserves investigation. Further clinical support for the hy pothesis was given in the same journal by MacGregor (1961), who reported 12 cases of polymyalgia rheumatica. One of those cases showed unequivocal clinical symptoms of temporal arteritis, but otherwise did not differ from the other cases in the series. The difference between polymyalgia and temporal arteritis might be explained by "the vessels involved rather than the disease which involves them. On the basis of similar clinical observations, Carlander (1961) and Olhagen (1963) shared this view Since the opposite opinion had previously been defended (Meulengracht 1945 and 1950 Holst & Johansen 1945), it is noteworthy that Olhagen (1963), *like Forestier and Certonciny (1953)*, categorically distinguished polymyalgia from periarthritis humeroscapularis, since, according to them, a *high E. S. R. excludes periarthritis humeroscapularis.*

Other authors with personal series have been less inclined to accept the hypothesis of arteritis in polymyalgia (Bagratuni 1956, 1957 1963 Todd 1961 Boyle & Beatty 1961 Berg & Lange 1963 Gordon et al. 1964 Andrews 1965). The main argument for this opinion was the absence of histological evidence of arteritis de Sèze et al (1964) felt that available data bout the possible role played by giant-cell arteritis in the causation of polymy algia rheumatica suggested the f llowing alternative hypotheses, *vi*. 1) polymyalgia is a manifestation of arteritis, 2) polymyalgia is a clinical syndrome of varying origin *inter alia* also temporal arteritis or the disease that causes temporal arteritis. Böttiger and Liljefors (1965) and Lange (1968) appear to embrace the second hypothesis. Lange is particularly critical and states that future research should try to find certain patho-anatomical and biochemical differences between polymyalgia and temporal arteritis, *i. e* try to eliminate the overlapping that appears to exist between the syndromes.

Like Lange, Smythe writes in his chapter on fibrositis in Hollander's Arthritis and Allied Conditions (1969) that polymyalgia rheumatica is a syn drome fighting for its existence. Smythe assumes also that "the proponents of the syndrome polymy algia rheumatica may have selected those elderly patients with fibrositis who happen to have a high sedimentation rate, arbitrarily gave their illness a new pseudospecific name, and exposed this high-risk group to unnecessary and unwise therapy It is thus obvious that there is strong reason for Lange s desire (1968) that authors defending diffe rent views present their series of polymyalgia rheu matica with as much relevant data as possible

Böttiger and Liljefors (1965) also feel that the liberal use of biopsy in polymyalgia is justified.

Articles, particularly old ones, not discussing the hypothesis of arteritis are obviously of less interest than those whose authors were well aware of the hypothesis at the collection of their series A few cases of histologically verified temporal arteritis in polymyalgia rheumatica have been published by a few French rheumatologists, namely Serre et al. (1961) and almost at the same time by de Sèze et al. (1961) and in England by Russell (1962). Later series in which the vessels were studied systematically are, however of greater interest, especially those where arterial biopsy has been done (Alestig *& Barr 1963 Skårset 1963 Hamrin et al. 1964* 1965 1968 Hamrin 1966, Kogstad 1965 Dixon et al 1966, Bruk 1967 Wilske & Healey 1967) In most of these series arteritis was very often de monstrated and other observations were made suggesting involvement of large and medium-sized arteries in the polymyalgic syndrome. In this connection it is of interest to note that cases with signs of aortic arch syndrome have, as previously mentioned, been observed very early in temporal arteritis (Jennings 1938) and that cases of aortic arch syndrome have been reported with increasing frequency in the polymyalgic syndrome (Carlander 1961 Alestig & Barr 1963 Hamrin et al. 1964

1965 Hamrin 1966, Serre et al. 1968). On the other hand, in recent research in the aortic arch syndrome increasing interest has been focused on, among other things, the occurrence of rheumatic symptoms in many of these cases during the "pre-pulseless phase" of the disease (Ask-Upmark 1956, Birke et al 1957 Sandring & Welin 1961 Strachan et al 1966, Roberts et al. 1969)

It should be mentioned that very recently a comprehensive review of giant-cell arteritis particularly from a clinical point of view has been published by Hamilton et al (1971).

CHAPTER 2

DESIGN OF INVESTIGATION AND SELECTION OF MATERIAL

NOMENCLATURE

The term temporal arteritis was introduced to designate clinical observation (Horton et al. 1932, 1934 Horton & Magath 1937), while the term giant cell arteritis was coined by a pathologist (Gilmour 1941) to describe 4 cases of arteritis that had apparently not been diagnosed *intra vitam* Here, the term temporal arteritis is used in its original clinical sense to denote a condition with clinical signs of a cryptogenetic inflammation of the temporal arteries. The term giant-cell arteritis is also used in the absence of both clinical and patho-anatomical signs of inflammation of the temporal arteries to designate such post-mortem inflammatory changes as are considered characteristic of temporal arteritis of the aorta and the large vessels given off by the aorta, and in arteries down to roughly the caliber of the temporal artery It has been shown that giant cells of the type in question are not specific of this type of arteritis. It is also known that giant cells cannot always be demonstrated in cases of temporal arteritis. The term giant-cell arteritis has also been criticised (Cooke et al. 1946, Jennings 1948). Here, however it will be used whether giant cells are demonstrable or not. Only in the description of the microscopic vessel changes will the term giant-cell arteritis be reserved for such changes in which giant cells have been demonstrated, while in the absence of such cells in the specimen, any inflammation of otherwise similar appearance will be termed uncharacteristic arteritis.

Several of the names suggested for the polymyalgic syndrome are well founded. Thus, for instance, the French suggestion rhizomélic inflammatory rheumatism in old age (Serre et al 1962) is a good descriptive name The term polymyalgia (Barber 1957), however appears to be so widely used and to be so deep-rooted that there is no reason why it should not be retained, especially since it is descriptive of the clinical picture In the present investigation the term polymyalgia arteritica (Hamrin et al. 1964) will be used (abbreviation. PMA). The name is, of course inadequate for those cases in which arteritis cannot be confirmed histologically But to simplify the presentation, the term will be used for all cases filling the diagnostic criteria and included in the material.

PURPOSE OF INVESTIGATION

Judging from the literature, in the beginning of the 60s (Chapter 1) much suggested that giant-cell arteritis played an important role in the causation of PMA Many interesting observations in different medical disciplines appeared to be explainable by assumption of a form of non-specific aortitis and arteritis, which was common, at least in elderly persons, and which was only occasionally fatal in the acute stage and therefore difficult to diagnose, and which manifested itself by above all, trivial and readily misdiagnosed "rheumatic" symptoms. The purpose of the present investigation was originally to examine biopsy specimens of the temporal artery systematically and, if possible, also of other expandable arteries to ascertain whether giant-cell arteritis is a component of the polymyalgic syndrome. The investigation was planned as *a prospective study* The first cases of PMA were diagnosed in March 1961 The investigation included a regular follow-up of patients, with special attention to any clinical signs of involvement of observable arteries, especially of the temporal artery

DIAGNOSTIC CRITERIA

When planning the present investigation it was decided to use the following diagnostic criteria, the first 5 of which were regarded as obligatory and the last 3 as facultative

1 Age above 50 years.
2. Occurrence of pain in at least 2 of the following 3 areas
   a) neck
   b) shoulder girdle
   c) pelvic girdle
3 Bilateral occurrence of the rheumatic symptoms
4 Dominance of this distribution of local symptoms during the active stage of the disease
5 E. S. R above 50 mm/1 hr (Westergren)
6 Duration of symptoms for at least .. months
7 Reduction of range of turning of the head and reduced mobility of the shoulders and hips.
8 In addition to raised E. S R. symptoms and signs of systemic disease: fatigue, anorexia, loss of bodyweight, fever and anaemia.

Comments on criteria

Criterion 1 The age limit was set at 50 years because, according to the literature the condition had been found practically only in persons above this age (see Table 3) Another argument for this age limit was that if the condition was a vascular disease, the predilection found for the higher age classes might not be true but only apparent, the disease in younger subjects possibly having other manifestations more difficult to recognise.

Criterion 2 The pain appears to be elicited by movements. Spontaneous pain during rest does not appear to occur in the disease. In the most acute cases even the slightest movement in any of the joints involved is very painful and is followed by an ching pain for some time. The duration of such pain appears to vary with its intensity It was also characteristic of the patients that during the active phase of the disease they woke up at night because changing of the position in which they were lying caused pain and wakened them It was characteristic that the pain was worse in the morning and abated in the course of the day Morning pain and stiffness of the joints were typical The pain was not always confined to the b. mentioned areas, but often also included adjacent areas In myalgia of the neck the pain often d over the crown and forwards towards the insertion of the sternocleidomastoid towards the mastoid process. Rheumatic pain in the upper arms and thighs belong to th. picture and some of the patients reported that the muscles "felt too short The muscles in the areas affected were tender to palpation though only slightly or moderately Tenderness was usually more intense around the large joints and over the insertions of the tendons. Many occasionally had severe pain around the knee joints, and examination usually revealed that these patients referred the pain to the area of the tendons of short and long biceps muscles laterally in the knee joint and still more to the medially inserting tendons of the semitendinous muscle, sartorius muscle and gracilis muscle (pes anserinus) A small area in the regions of the greater tubercle of humerus and greater trochanter of the femur was often tender

Criterion 3 The requirement of symmetric localisation of the pain implies that the shoulders and/or the hips should be affected bilaterally during the disease As for the intensity and duration of the pain, however large differences between the sides were tolerated All variations were thus accepted, from severe pain in both shoulders and/or hips, large differences between the sides, and mild symptoms on both sides. Also a chronological difference between the time of onset and the severity of the local symptoms on either side was tolerated.

Criterion 4 The disease sometimes made its appearance in the form of pain occurring in influenza, but was gradually confined to the neck, shoulders and hips within a few days. Sometimes it was the distal parts of the limbs that were first affected, but these symptoms were of much shorter duration than the pain appearing in the same site but later in the disease.

Criterion 5 In many cases the *E. S. R.* had reached its highest level before the disease had been diagnosed, and in some cases this value had been noted before admission of the patient to hospital.

Criterion 6 The duration of at least 2 months refers to the entire period of pain with its characteristic distribution over the shoulders, hips and neck.

Criterion 7 Desirable, though not necessary for the diagnosis was limited mobility of one or more of the following joints cervical spine, shoulders or hips. In an early stage of the investigation it was realised that in many cases the disease had passed its climax before it had been diagnosed and the

mobility had by then improved. Notes were therefore made not only of the objective limitation of movement found at the examination, but also of the patient's report of his condition before the examination and any information from the preclinical phase of the disease, in order to find out any previous impairment of mobility.

Although this belongs to the description of the course of the disease, it should be stressed — since the diagnosis had been made in different stages of the disease — that the reduced mobility which occurred in an early stage in the large joints was probably different in nature from the pain that persisted or that was not observed until later in the course. In the beginning of the disease the reduction in mobility appeared to be due to pain on active movement. This was apparent from the fact that on slow careful passive manipulation it was possible for the joints to be moved through an unexpectedly large angle, e. g. a shoulder joint, which initially appeared to be completely stiff. In this stage the impairment of mobility also varied widely in the course of the day and was greatest in the mornings. The range of movement could be rapidly increased by the use of analgesics and particularly by local or systemic steroid therapy. A limitation of mobility that persisted or possibly became worse later in the disease could not be improved to the same extent by such drugs. In such cases there was generally muscular atrophy, especially around the shoulder joints, and passive extension was then prevented by absolute resistance which seemed to be of mechanical origin. In this stage the condition could not be distinguished from what is generally known as a frozen shoulder (Codman 1934, Simmonds 1949, Lippmann 1951, Lundberg 1969).

Criterion 8. Reported fatigue, anorexia, loss of bodyweight and prolonged fever were regarded as lending good support to a diagnosis of PMA.

DISCUSSION OF DIAGNOSTIC CRITERIA

de Sèze et al. (1965) pointed out that although unanimity had been achieved concerning the definition of PMA, opinions differed widely on the classification of the disease. This lack of agreement persists still to-day. As early as 1961, when the present investigation was planned, clinicians, who published their cases under different names, appeared to agree that it was a fairly well defined syndrome. No strict criteria had been used for the diagnosis at that time and the diagnosis of the syndrome was based on more or less detailed descriptions of the clinical picture.

Most authors had observed symptoms also of the knees, elbows, hands and feet (Porsman 1951, Kersley 1951, Meulengracht & Schwartz 1952, Bagratuni 1953, 1956 and Gordon 1960). The occurrence of symptoms in the distal parts of the limbs during the disease were therefore also accepted in the present investigation.

Rigorous criteria were decided upon from the very beginning because it appeared à priori reasonable to assume that the more rigorous the criteria, the more informative and reliable the results would be. The criteria were thus more rigorous than those set up by de Sèze et al. (1965). According to the French authors, the diagnosis of PMA could be made if 4 of the following 6 criteria were satisfied: 1) age above 50 years, 2) pain of a certain character in the shoulders, 3) pain of a certain character in the neck or 4) hips, 5) raised E. S. R. and 6) regression within 1–2 or more years. In the material reported by de Sèze et al. (1965) one of the 45 patients was below 50, only 23 had an E. S. R. above 50 mm/1 hr, which means that about half of their patients would not have been acceptable in the present series.

When planning the present investigation it was thought possible to make the diagnosis on the basis of the clinical picture and raised E. S. R. alone. Attempts were therefore made to diagnose cases before the results of laboratory tests and arterial biopsy were known, but this did not prove possible in all the cases. Since a raised E. S. R. and electrophoretic abnormalities are common to the syndrome and to certain forms of renal cancer, patients were examined urographically from the beginning, and this was done in all cases except one case in which the patient suddenly died from cerebral haemorrhage. Because of the raised E. S. R. and the clinical picture in general more comprehensive investigation had been started or performed in some cases before the diagnosis of PMA. In other cases, however, special examinations were considered unnecessary and, unless otherwise indicated, were not performed.

SELECTION OF CONTROLS

As pointed out in the preceding chapter, stenosing processes or aneurysms of the large arteries have sometimes been observed in patients with clinical

temporal arteritis (Jennings 1938, Andersen 1947 and Palm 1958) Similar observations have later been reported in polymyalgia rheumatica (Carlander 1961) and giant-cell arteritis (Alestig & Barr 1963) In the spring of 1963 the author observed the development of an aortic arch syndrome in a patient with polymyalgia in the active stage. Later signs of aortic arch syndrome were observed in several cases (Hamrin et al. 1964 1965 Hamrin 1966). These cases were surprising It was therefore considered of interest to compare a control series regarding clinical signs of stenosing processes of the large arteries. In 1964—1965 a control series was collected from patients admitted to Växjö hospital.

The requirements set up for acceptance of a control were based on the following considerations. As known, rheumatic symptoms in the broadest sense of the term are common and, with time, affect almost everybody For any clinican well acquainted with PMA the disease is readily recognised during the active stage. In clinical work one sometimes encounters also patients whose history contains such detailed information about previous periods of disease that it is possible in retrospect to make a diagnosis of PMA. Often, however the notes of previous rheumatic disease are less informative and poor in details and then do not permit a reliab differential diagnosis. This applies also to the fragmentary descriptions given from memory by elderl persons who have had previous spells of rheumatic symptoms. It therefore appeared to be meaningless to try to decide the type of earlier rheumatic symptoms with anything like certainty The first requirement for acceptance of a person as a control was therefore complete freedom [illegible] or present rheumatic symptoms or signs. [illegible] had not only any typical sympto[illegible] had even never had any symptoms [illegible] motor system, as judged from an [illegible] mination of earlier hospital [illegible] this simple requirement it was [illegible] a control series. This is also [illegible] from the Arthritis and Rheumatism [illegible] Research and the British Rheumatism and Association, according to which only two people in a hundred in Britain can hope to escape some form of rheumatism and arthritis by the time they are seventy" (Nature 1968) It appeared very difficult to obtain control cases from the department of internal medicine but much easier to obtain them from the department of surgery

The nurses at the departments of internal medicine and surgery were requested to report to the author all patients in their department who satisfied the following requirements.

1 Age above 50
2. No previous or present rheumatic diseases or rheumatic symptoms Here rheumatism is to be understood as any sort of pain of the muscles, tendons or joints.
3 Never previously received physio-therapy or short wave or roentgen treatment because of pain
4 Never sustained any major injuries involving the large joints.
5 No signs of advanced malignant tumours.

The nurses were informed that it would probably be difficult to find sufficient controls in the highest age classes, but that it was especially desirable to obtain such cases. All in-patients wh[illegible] thought satisfied these requirements w[illegible] [illegible]ination. The patients were [illegible]ing their present disease and [illegible] earlier diseases, special [illegible] symptoms and [illegible] pain. Before a patient [illegible] had to satisfy the foll[illegible] [illegible] 9.6 g/100 ml and [illegible] region of th[illegible]

[illegible] [illegible]ly selected [illegible] out o[illegible] [illegible]uch aft[illegible] by [illegible] beca[illegible] lysis of [illegible]

MATERIAL AND METHODS

COLLECTION OF PATIENTS

The series consisted of in patients of the department of internal medicine at the Central hospital of Växjö, who filled the criteria for a diagnosis of PMA (see Chapter 2). The collection of the material covered the period 1/3 1961—31/8 1968 *i e 7 ½* years.

Växjö hospital is a central hospital for the County of Kronoberg, a district in the south of Sweden, which in 1965 had a population of 158 695. Despite the urbanisation during the last two decades most of the inhabitants are still living in rural areas or in small towns (<5 000 inhabitants). During the last 10 years the district has received a number of immigrants from South-Europe. For many years before that time inhabitants had been leaving the district. The older population is therefore ethnically very homogeneous. All of the patients are Scandinavians and most of them are living in villages or small country towns.

The district has not only the central hospital in Växjö but also other hospitals and some homes for the aged and chronically sick. It is therefore difficult to say the exact size of the population catered for by Växjö hospital, but it is probably somewhat more than 100 000 inhabitants.

During the major part of the collection of the material the department had 110 beds, and 6 physicians who also served at the out-patient department. Since the number of physicians was low for the number of inhabitants in the district, it was difficult for the in- and out-patient departments to cope with the requirements of the population. During the aforementioned period the author was in charge of less than half of the in-patients, but also had a considerable amount of consultative work at the clinic. Interest in the disease gradually grew also among physicians in and outside the hospital. Unfortunately this favourable fact was counteracted by the fairly rapid turnover of young colleagues. The interest in rheumatic diseases has always been fairly keen at the department and despite the overburdening of the hospital admission of such patients was fairly liberal. Neither did high age disqualify admission. During the collection period the hospital had the following special departments: internal medicine, paediatrics, infectious diseases, surgery, gynaecology, otology and ophthalmology, diagnostic roentgenology and clinical chemistry. The following specialities were, however, not represented: psychiatry, neurology, dermatology, rheumatology, orthopaedic and pathology.

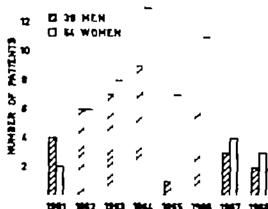


Fig. 1. 93 cases of PMA diagnosed in 1961—1968 at department of internal medicine, Växjö hospital.

During the period of collection PMA was diagnosed in 94 cases, but as will later be apparent, the diagnosis in one of the cases was thought to be false (*vide infra*) in 1965 that case was excluded from the material, which thus consisted of 93 patients (39 males and 54 females). The sex distribution of the annual number of cases diagnosed is given in Fig. 1. The increase from 6 cases in 1961 to 22 cases in 1964 reflects the increasing interest in the disease at the department. The lower frequencies in 1965, 1967 and 1968 may be explained by the fact that the author was away from work during half of the time and that no new cases were added during the last 4 months of the last year. The sex distribution varied from year to year, which may be explained by the fact that during certain periods the author served at the male department and at others at the female department.

The ages of the male patients varied between 51 and 80 years and those of the females between 51 and 84 years. The mean age for the entire material was 67.9 years (Fig. 2). The median age for all patients was 69.7 years.

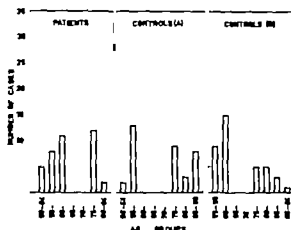


Fig. 2. Age distribution of 93 patients with PMA and of 96 controls (A). Of the controls, 71 were re-examined after almost 2 years (B).
Mean ages of patients 67.9 of controls (A) 68.5 and of controls (B) 68.7 years.

Comments on selection of patients

The diagnostic criteria were such as to require cooperation of the patient Therefore, no attempts were made to diagnose the condition sometimes suspected in unconscious patients, in patients with advanced sen le dementia and in mentally deficient patients Patients with myocardial infarction some times show suspect signs of PMA such as protract ed subfebrility persisting raised E. S R in asso- tion with myalgic symptoms or shoulder periarth- ritis (compare similarity with Dressler's syndrome — Dressler et al 1957) Though the results might have been interesting, no patients with myocardial infarction were examined for PMA

An exception to the above principles was, how ever case 91 a man who was 73 years on admission because of cerebral haemorrhage and who died 4 weeks later from the lesion Two days after the vascular insult the E. S R. was 103 mm/1 hr suggesting the coexistence of another disease Data obtained from relatives and physicians who had seen the patient during the last two years allowed a very probabl. *ante mortem* diagnosis of PMA With the crit ... et up recognition of PMA in the age range ... ion offers no difficulties Two ... however be made Occasional ly the ... red ... question and fills ... considerab ... the limbs are ... whether the cl ...

toms in the area of the neck, shoulders and pelvic girdle Such cases closely resemble rheumatoid arthritis. They were not included in the material and were not studied further More often — at least in the out-patient department — are those cases which resemble PMA but are easier to delineate because, despite prolonged observation they did not fill the criteria *i e* symptoms in at least 2 of 3 regions, or bilateral symptoms in the shoul ders and hips. As for rheumatic symptoms they may be characterised as incomplete polymyalgia. Such cases were not included in the material either

As mentioned in Chapter 2, attempts were made to diagnose the cases merely on the basis of clinical criteria and a high E. S R In none of the cases had the patients been examined serologically be fore establishment of the diagnosis The material included 10 cases primarily admitted to the depart ment for infectious diseases In these cases poly myalgia had been diagnosed or suspected before the patients were referred to me In 6 of these cases (Nos 17 18 25 31 81 and 86) biopsy had con firmed arteritis in 4 cases, but not in the remain ing 2. Arterial biopsy had not been performed in any of the other cases before clinical diagnosis and inclusion in the material

The appearance of clinical signs of temporal ar teritis or suspect signs did not exclude PMA On the contrary a systematic search was made for such symptoms.

EXAMINATION OF THE PATIENTS

Before the diagnosis of PMA had been established and the patients accepted in the material, the author himself took a thorough history Many of the patients found it difficult to recall the past because of their poor general condition and sometimes high age The history was supplemented, especially in such cases by interviews with relatives and people taking care of the patients Information in the cli nical records at hospitals where the patient had previously been cared for were examined and utilised. As the interval between the onset of the di sease and admission to the clinic varied from weeks to months, sometimes years, serious endeavours were made to obtain as much information as pos sible from the preclinical period of the time of the disease Interest was focused in particular on the initial stage. Colleagues at the out patient depart ment also placed *their records at my disposal.* In

many cases the E. S R had been d rmined on one or several occasions before admission to hospital Information on these E S. R. determinations were obtained and included in the present study After admission to hospital inquiries were repeatedly made into the history of the patient together with the patient and sometimes his relatives, when supplementary data were obtained and corrections, if necessary were made. It was remarkable how much easier it was for the patient to give a better history after improvement of his mental condition following a few days treatment with steroids.

Before a case was accepted the diagnosis had to be made or confirmed by the author Both during the time the patient was in hospital and the duration of the follow-up at the out patient department, these patients were looked after exclusively by the author As soon as the diagnosis had been made the patient s hospital card was given a special number The patients were thus numbered chronologically as they were accepted in the material. There were 4 exceptions, Nos 86, 88 89 and 90, in whom the diagnosis was made in 1964 but who were not given numbers until the end of the collection period. A further exception was patient 34 in whom the diagnosis was made later than that indicated by her number she substituted the aforementioned case that was excluded from the material in 1965 The patient s number thus gives a rough idea of the period of observation The first 23 diagnosed cases kept their chronological numbers from the very beginning (Hamrin et al 1964).

The patients' histories were taken in the uniform way the author systematically questioning the patients regarding the symptoms necessary to satisfy the criteria. Since, in several cases, the disease had passed its climax by the time of the diagnosis and the pain had abated, questions concerning rheumatic symptoms often gave a surprising and good insight into the severity of the disease. Such questions, capable of illuminating the existence of pain and impaired range of movement of the neck, back, shoulders and hips, concerned the patient's ability to get out of bed without aid, to walk with and without support and to walk up steps and get up from a chair Answers to such questions as to the patient s ability to put on his jacket or dress and apron, to comb himself to shave or to eat without help also gave good information of the function of the shoulder joints. Difficulty in putting on stockings or shoes revealed impaired movement of the hips. The tendency to turn the body when looking to one side suggested impaired movement of the cervical spine.

In the clinical examination attention was directed to the organs of locomotion and circulation especially the arteries. The clinical examination of the arteries is dealt with in Chapters 5 9 and 10

At every bed-side examination notes were made of any atrophy of the musculature of the shoulder and pelvic girdle and the range of movement of the following functions was studied

turning of head

in the shoulder joint abduction (outward upward elevation) and rotation with upper arm abducted 90 and elbow flexed 90

flexion, abduction and adduction and rotation of the hips.

The limitation of these movements was visually estimated in degrees, but sometimes it was only noted in the records whether the range of movement had improved or become worse since the previous examination, or the impairment of mobility was simply described as mild moderate or severe, especially concerning the hip joints. More exact measurement of the impairment of mobility would have been of only limited value because the impairment was due mostly to pain which, as mentioned, varies widely in the course of 24-hours

The mobility of the cervical spine was said to be impaired if it could not be passively turned more than 60° in either direction or one direction, and of the shoulder joints if the arms could not be passively abducted to 180 in the frontal plane, or if the total rotation was less than 160° No attempt was made to set up limits of the normal range of movement of the hips since many of the patients obviously had coxarthrosis, sometimes of clinical significance When it was doubtful whether the limitation of movement was due to arthrosis or polymyalgia a detailed inquiry was made into the previous course If the limitation of movement of the hips had occurred in association with the patient's present disease and decreased in association with general improvement of the patient with or without steroid therapy such improvement was taken as a sign that the impairment of function was due partly or entirely to PMA

I order to obtain a better survey of a long and variable course of such a disease as PMA in the individual case and in the series as a whole, a diagram was set up for each patient and kept up to

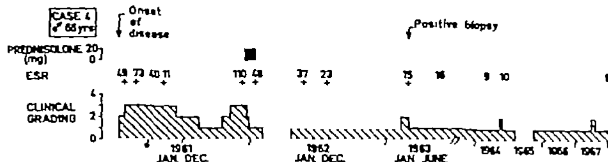


Fig. 3 Graphic demonstration of course in case 4. Clinical grading, as judged from intensity of pain and reduction of mobility essentially according to Gordon (1960). Grade 4 severe pain with reduced mobility of neck, shoulders and hips. Patient severely disabled. Grade 3 moderate pain with reduced mobility of at least one of these joints. Grade 2 mild, but constant, pain requiring continual use of analgesics. Grade 1 mild, inconstant pain requiring analgesics at most occasionally.
↓ denotes time of diagnosis.

date during the observation period. According to the myalgic symptoms and range of movement of the systematically examined joints, the rheumatic symptoms were graded as follows

G ade 4 Severe myalgia and periarticular pain in the neck, shoulders, upper arms and thighs. Reduced mobility of the cervical spine, shoulders and/or hips when examined in the way described above. The patient was severely disabled and could not manage the daily physical activity of life without help

Grade 3 Moderate pain in the regions described above Limitation of movement of one or more of the examined joint functions. Only occasionally in need of help to manage daily life

Grade Mild, constant symptoms. No limitation of movement of the joints examined. No disability

G ade 1 Mild, inconstant symptoms. Rarely if ever in need of analgesics.

G ade 0 No rheumatic symptoms.

This scale was used by the author in previous papers (Hamrin 1966, Hamrin et al 1968) and is based largely on an investigation by Gordon (1960), who stated t is admittedly difficult to assess subjective symptoms in a manner such as this, but there is no other satisfactory method of recording the varying severity of the pain during the course of the disease It should, howev r be mentioned that this *gradation is not entir l subjecti e because grades* 3 and 4 require limitation of mo ement of one or more of the joint functions studied. In addition to this gradation of the rheumatic symptoms, the above mentioned diagram included also the date of onset of the disease, the diagnosis and biopsy of arteries as well as the E. S. R. and steroid therapy given. As in other selected case reports in this book such a diagram (Fig 3) will illustrate the following case report exemplifying moderate and typical cases of PMA

Case 4 A L. Fig. 3) — *The patient* was a 66-year-old, retired and previously healthy elementary school teacher I the middle of January 1961 and without any previous infection he fell ill with fatigue, pain and tenderness in the musculature of the buttocks and thighs, especially the flexors on the dorsal side of the thigh. He found it difficult to get up from chair He also soon had pain in the right shoulder After 1 *month illness he was admitted to the department of internal medicine where polymyalgia rheumatica was diagnosed* H spent nine weeks in hospital. In the beginning he became worse and the shoulder joints became increasingly stiffer He walked with dragging feet, all movements were painful and careful. His gate resembled that of patients with Parkinson s disease but he had no tremor The range of abduction of the shoulders decreased so that he had to be fed, but he could none the less write on his typewriting machine. He was slightly subfebril and his temperature seldom exceeded 38 The E. S. R. was about 70 mm/1 hr in 1961 He had eosinophilia 500, 769 and 506 per µl, respectively Despite absence of positive signs of neurologic disease, such as neckstiffness and headache, the cerebrospinal fluid was examined at intervals of weeks. First specimen 14 white blood cells/3.2 µl and total protein 85 mg/100 ml second, 4 white/3.2 l and total protein 56 mg/100 ml.

While in hospital he lost 8 kg, and during the first year of his disease, all together 14 kg. A muscle biopsy specimen from the calf showed nothing remarkable. When he left hospital in April 1961 his condition was unchanged, except that myalgia of the thighs and hips had abated. He afterwards improved fairly quickly The range of movement of the shoulders increased.

In the autumn of 1961 he felt worse, he was again subfebrile and the E. S. R. rose to 110 mm 1 hr Myalgia recurred, but was not so severe as t onset Steroid therapy was started and produced a prompt effect. The dose was successively reduced and fter half a year it was down to 1—2 mg prednisolone day on the average. Steroid therapy was then withdrawn for 2 weeks, and in February 1963 muscle pain returned. *Neither then previously or later had the patient headache or temporal pain.* On palpation both temporal arteries felt normal. After he had had the disease for 2 years and been treated with steroids for 1 year *biopsy specimen* was obtained of the left temporal artery Examination revealed *giant-cell arteritis.* During the following years the patient was given a maintenance dose of steroids, corresponding roughly to 1 mg prednisolone per day Occasional tentative withdrawal was usually followed by accentuation f the otherwise ery mild symptoms of myalgia.

When the patient had been ill for somewhat more than 3 years I auscultated his peripheral arteries for the first time in spring 1964. A bilateral strong murmur suggesting stenosis was heard over the axillary and brachial arteries. Over the subclavian arteries only a weak systolic murmur was heard. N murmur was heard over the heart. From the very beginning of the disease, the blood pressure was measured bilaterally No significant difference, (*i.* ≥25 mg Hg systolic pressure) was noted between the arms on any occasion up to 1969

Continued observation of patients

All the patients were admitted on at least one occasion and several two or more times to the department of internal medicine I addition, the patients were followed up at short intervals at the out-patient department as soon as their condition required, or as they wished All the patients also appeared for control examination when desired for the present investigation In 1967—1968 all patients except 11 who had died before 1968, were examined on at least one occasion on which various samples were obtained for laboratory analysis. As for the frequency of observations, reference is made to the chapter on arterial murmur (Chapter 9), which gives the frequency of follow-up at the systematic auscultation of arteries, which lasted from 1964—1968 The examination frequency was about the same during the first three years 1961—1963

It may be justly objected that the diagnostic criteria for PMA are crude because they are based mainly on qualitative, clinical phenomena, but they illustrate also the difficulty encountered in classification of rheumatic diseases. As in all clinical work, however the regular clinical follow-up of the patients mplies a continuous and critical examination of the diagnosis and the possibility of detecting any erroneous diagnosis and concomitant diseases But the diagnosis was revised in only one case. As previously mentioned, one patient was thus excluded from the material during the collection period.

In that case a successive swelling of the neck was observed after 4 years' disease and the swelling proved to be tuberculous lymphoma. Eight years after the primary onset and 4 years after the diagnosis of the tuberculous lymphoma, which was cured by adequate therapy the patient died from a ruptured aortic aneurysm. At post-mortem examination (see Appendix) non-specific aortitis and arteritis of the large vessels was observed.

When I saw this case for the first time in the autumn of 1963 the woman had been ill for slightly more than 2 years and during this period the E. S. R. had always been about 100 mm at close follow-up The woman had no convincing symptoms of rheumatic nature and her reports about such symptoms were difficult to judge because of her mental debility and suggestibility It was not until after long observation that the patient was included in the present material and then mainly because of certain dilatation of the aorta observed during the years 1961—1963 when the lungs had often been -rayed, but never revealed anything remarkable.

This case was thus erroneously excluded from the material. It illustrates the weakness of the diagnostic criteria which require a certain cooperation of the patient, especially as in this case after 2 years disease the patient showed no objective signs of rheumatic disease The case is included in a previous series reported by the author (Hamrin et al. 1965).

Duration of disease before diagnosis

The duration of the disease before the diagnosis varied widely (Table 4). In one third of the cases PMA was diagnosed within 3 months and in one half of the cases within 6 months of onset In 84 (90) of the cases the disease was diagnosed within 18 months of onset. Nine (10 /) of the patients had been ill for more than 2 years before the diagnoses. I several of these cases the course had been long and exacerbating. In 3 of them there

Interval between clinical onset and diagnosis (months)	Men	Women	Total
0— 3	12	19	31
4— 6	9	11	20
7— 9	12	7	19
10—1	2	5	7
13—18	3	4	7
19—24	0	0	0
>24	1	8	9
	39	54	93

Table 4 93 cases of PMA grouped according to interval between clinical onset of disease and diagnosis.

were signs of aortic arch syndrome and 2 of them had been ill for more than 5 years before they had been diagnosed. One of them, No 41 had been ill for 9 years and another No 34 for at least 12 years.

Observation period

Here observation period is to be understood as the interval between the diagnosis of PMA in a given case, *i e* its acceptance in the present material and the last physical examination of the patient before Jan. 1 1969 The observation period varied between less than 1 month to 87 months and the mean for this time was 33.6 (± SD 22.08) months. No significant difference was found in this respect between men and women.

COLLECTION OF CONTROLS

The control series consists of 96 persons of whom 45 (47) were men and 51 (53) women. Only persons satisfying the criteria set forth in Chapter _ were accepted. About two thirds of these were selected among in-patients of the department of surgery and one third among patients from the department of internal medicine The main diagnoses in these cases are given in Table 5

The controls were collected and examined between 1964—1965 for a comparative physical examination of the peripheral arteries. Since this comparison with the polymyalgic patients distinctly argued for a sign cantly higher frequency of stenosing processes in the latter material it was considered desirable re-examine the controls. 1—3 years after the examination the controls were therefore requested to present themselves for re-examination. At the second examination of these controls special attention was given to the peripheral arteries as at the first examination Blood samples were also obtained from the controls at this re-examination for the same laboratory analyses as in the patients.

In contrast with the first examination of the controls the second was performed at the out patient department. Several of the controls had died in the meantime while others because of disease or high age could not participate. Seventy one (73) of the 96, however were re-examined in 1966—1968 The interval between the two examinations of the controls varied from 12 to 35 months. The mean was 27.2 months (± SD 5 15). Neither at the first nor at the second re-examination of the controls did the latter differ substantially in age or sex distribution from the patients (Fig. _). The range of variation of the age was, however somewhat wider for the controls than for the patients with relatively more individuals in the lower and higher age classes at both the first and the second examination.

	Males	Females	Total
Biliary and pancreatic diseases	2	10	12
Surgical d eases of urinary tract incl. chronic pyelonephritis	9	3	12
Peptic ulcer	7	4	11
Malignant tumours	3	3	6
Fractures, commotio cerebri	1	5	6
Acut abdomen + hernia	1	4	5
Diseases of colon and rectum	2	3	5
Crural thrombosis and ulcers	1	3	4
Cardiovascular diseases	8	5	13
Diabetes mellitus	4	2	6
Blood diseases		2	4
Bronchial asthma, Löffler's syndrome	3	1	4
Dermatoses	1	2	3
Endocrine diseases	0	[illegible]	2
Intoxication	1	0	1
Pneumonia, Osler' disease	0	2	2
	45	51	96

Table 5 Main diagnoses in the 96 patients selected as controls.

BIOPSY FINDINGS

INTRODUCTION

The possible relation between polymyalgia and temporal arteritis was raised in the 1950s and was the subject of extensive debate in the 1960s. As pointed out in an Editorial in the Lancet in 1961 the absence of reported cases of temporal arteritis in polymyalgia rheumatica might be due to a question of classification, i. e. some cases of giant cell arteritis involved only the cranial arteries and were then diagnosed as temporal arteritis, while in other cases of giant-cell arteritis the aorta and large arterial trunks other than the cranial arteries were attacked with the possible development of clinical picture resembling that of polymyalgia rheumatica. Also the possibility that different arterial regions were affected at different stages of the disease appeared plausible (Paulley 1956, Kersley 1956, Paulley & Hughes 1960 Russell 196..) Under such circumstances the relation between the diseases might easily escape attention. Generally speaking, it is difficult to draw a distinct line between the clinical and subclinical course of a disease, which will depend on, among other things, the frequency with which a patient is examined. This is obvious also from the literature on the clinical course of temporal arteritis in which the rheumatic symptoms are often mentioned only incidentally and briefly In polymyalgia one might likewise imagine that the symptoms of involvement of cranial arteries are so mild or transient that they readily escape attention In addition, one cannot exclude the possibility of asymptomatic involvement of arteries.

Since the purpose of the present investigation was to find out whether giant-cell arteritis is a component of polymyalgia, it would be only natural to focus clinical interest on symptoms of the arteries. Initially interest was therefore directed to the temporal arteries. The bulk of the biopsy specimens consisted of segments of this artery which is easily accessible for biopsy The possibilities of obtaining biopsy specimens of other arteries of desired caliber i. e. at least the caliber of the temporal artery are limited by the risks and by the inconvenience to the patient. During the first few years of the present investigation, however specimens were sometimes obtained also from arteries other than the temporal artery The biopsy specimens from the first 54 cases were examined at the department of pathology in Lund (Associate Professor N Jonsson) In the remaining cases the specimens were examined by Dr G Östberg at the department of pathology Malmö The histological findings in some of the cases have been reported in previous publications (Hamrin, Jonsson & Landberg 1964 1965 Hamrin 1966 and Hamrin, Hellsten & Jonsson 1968)

Choice of time of arterial biopsy

Experience with the first 7 patients selected for biopsy of the temporal artery influenced the time of biopsy of the arteries in later cases (Table 6) Arteritis of temporal arteries could evidently run an asymptomatic course i. produced no local symptoms It could also cause extremely mild symptoms, difficult to trace, or moderate and severe symptoms up to temporal arteritis with severe temporal pain and infiltrated reddened temporal arteries, tender to palpation (case 15). By the time the symp-

Case No.	Sex/ Age	Highest ESR	Temporal symptoms and signs¹)	Interval in months between onset of PMA and TA	TA and biopsy of temporal artery	onset of PMA and biopsy of temporal artery
1	M 73	155	0	—	—	1
3	F 73	135	(★)	2	1	3
12	F 73	133	(★)	5	5	10
15	M 65	64	+	13	0	13
17	M 59	125	★	2	0	2
18	M 66	128	★	1	0	1
23	F 68	146	(★)	0	2	2

Table 6. Time-relationship between onset of polymyalgia arteritica (PMA), symptoms and signs of temporal arteritis (TA) and biopsy of temporal artery in the first biopsied cases of PMA. The microscopical examination of the arteries regularly showed inflammatory changes.

¹) + denotes classical clinical picture of TA, ★ suspect symptoms of TA in history and/or at physical examination, (★) only vague memory of any symptom in temporal region. Ordinary pulsations of temporal artery and its branches· 0 no history or signs of TA. Further details are given in Chapter 5

toms of temporal arteritis had appeared in case 15 the symptoms of myalgia had considerably improved (Chapter 7) The course suggested that the arteritis would probably not have been diagnosed histologically if the temporal artery in this case had been biopsied before the appearance of the clinical temporal arteritis, which occurred at least one year after the onset of polymyalgic symptoms

During the following years the time of biopsy of the temporal artery was decided upon in the following way As soon as the polymyalgia had been diagnosed, a biopsy specimen was obtained of the temporal artery if temporal symptoms could be traced in the patient's history even if such symptoms had been only mild and transient or extremely mild. In the absence of such symptoms biopsy was postponed until such symptoms might appear If no such symptoms appeared in the temporal region, a biopsy specimen was nevertheless sooner or later obtained. Since it was necessary to inform the patient why such biopsy was desirable, the duration of expectancy before biopsy was decided by the clinical course Attempts were therefore made not to wait so long until the disease had shown signs to abate Since literature studies had revealed that postarteritic changes may be difficult to distinguish histologically from arteriosclerosis it was considered unwise to postpone biopsy too long

Some of the patients had received steroid therapy before polymyalgia had been diagnosed In other cases steroid therapy was, when possible, postponed until after biopsy In the absence of special contraindications the patients afterwards received steroid therapy whether biopsy had proved positive or negative. But it was not always possible to refrain from steroid treatment before biopsy Postponement of steroid therapy in cases without local temporal symptoms placed the author in a dilemma between the desire to obtain as exact a diagnosis as possible and the desirability to give as effective palliative treatment as possible This conflict was, however mitigated by my attitude during the first few years of this investigation, viz. that in the age classes in question steroid treatment involves fairly severe risks.

Considerations on diagnostic biopsy of the temporal artery

In most cases the temporal artery and its branches could be palpated through the skin before biopsy The pulsations were, however sometimes strikingly weak. In a few cases localisation of the artery was facilitated by tenderness along its course and by small nodosities in the vessel walls Before induction of infiltration anaesthesia the course of a selected vessel was marked with a fine scratch of the skin In most cases the frontal branch was selected, though occasionally the parietal branch was preferred After the vessel had been exposed attempts were made — sometimes after extension of the incision — to include a piece of the main trunk in the specimen. In this connection it might be mentioned that the site of the bifurcation of the temporal artery into a frontal and parietal branch varies somewhat. It is therefore sometimes necessary to refrain from trying to obtain a piece of the main trunk in order to avoid coming too close to the facial nerve In several cases the specimen consisted only of a segment of one of the branches. The length of the excised segments varied between 1 and 6 cm.

Surgical exposure of an uninflamed temporal artery can be performed without difficulty by even a surgeon less well aquainted with the operation, but experience with the operation is an advantage for identifying an inflamed artery Lack of such experience probably explains why it is often to be read in published case reports that attempts to obtain a representative biopsy of the temporal artery proved unsuccessful. In order to find a markedly changed vessel the operative field must often be explored very carefully The operation is therefore sometimes very timeconsuming The patients did not appear to find the operation so very disagreeable The skin incision was closed with an atraumatic needle and nylon. After a few months the scar was barely discernible, and later it could be seen only with the aid of a loupe

The choice of the side from which the specimen was to be obtained was decided mainly by the following factors. When the cranial symptoms were predominant or occurred on only one side, that side was chosen. In the absence of cranial symptoms, that side was chosen on which the symptoms in the neck or shoulders were predominant. In some patients there was tenderness along the carotid artery on one side and then that side was chosen for biopsy If the symptoms were roughly equal on both sides, neither side was given preference

[1] Practically all of the biopsies were performed by Dr T Landberg and Dr S. Hellsten.

Biopsy of other arteries

In some cases biopsy specimens w re obtained from other arteries, namely occipital artery circumflex scapular and superior gluteal artery as well as second perforating from the femoral artery

The caliber of the occipital artery is roughly the same as that of the temporal artery while that of the circumflex scapular artery is somewhat smaller Both these arteries are seated deeper than the temporal artery as is also the second perforating artery from the femoral artery But these arteries are readily accessible. It is more difficult to explore the superior gluteal artery which is a branch of the internal iliac artery and leaves the pelvis through the suprapyriform foramen. This was the largest of the vessel resected.

BIOPSY SPECIMENS

Arteries

The temporal artery was biopsied in 84 of the 93 cases. In the remaining 9 no biopsy specimen of any artery was obtained. This was because 6 of the patients had improved or recovered before contemplated biopsy and 2 (Nos 49 and 91) died before planned biopsy (in these 2 cases arteries were examined microscopically post mortem so that histological examination of arteries ha e been performed in all together 86 cases). One (No 74) of the patients was a woman who had an endogenous depression and who refused diagnostic biopsy Of the above 84 cases, the temporal area on the other side was explored in 12 after an interval of 1—20 months (average 9 months) In 4 of these 12 cases either the first or the second biopsy specimen contained small arteries not representative of the temporal artery or its main branches. This was at the first operation in 3 cases (Nos 38, 59 and 82) and at the second in 1 (No 65). In the first 3 cases the operation had been performed by one inexperienced surgeon and in case 65 no pulsating essels could be palpated before or after exploration of the temporal region Since the entire area was carefully explored and since no structures resembling the temporal artery were found, it must be assumed that in this case the artery was markedly changed (Chapter 8).

All together then, 92 representative specimens were obtained from the temporal artery and/or one of its branches in 84 of the 93 cases.

I 12 of the 84 cases in which a specimen was obtained from the temporal artery all together 16 specimens from other arteries were also obtained for microscopic examination. These extra specimens were sometimes obtained at the same time as thos of the temporal artery but more often on a later occasion The biopsy material consisted of specimens of 108 arterial segments from 84 patients. 92 were specimens of the temporal artery of the occipital artery and 14 of extracranial arteries.

Veins

The veins were not examined systematically Concomitant veins of the temporal artery were examined in 3 cases and of the circumflex scapular artery in .. In case 67 thrombosis of a large subcutaneous vein in the right arm occurred in the 10th month of the disease. The thrombosis extended from the back of the hand up to the axilla, and a biopsy specimen of this vein was obtained from the lower arm.

Skeletal musculature

From 15 patients 18 muscle biopsies were obtained m. quadriceps (4 cases), m. temporalis (4 cases), m teres major (3 cases), m biceps femoris (? cases), m gastrocnemius (2 cases) and m. sterno-cleido-mastoideus in 1 m. rectus abdominis and m tibialis ant in 1 Thus 8 biopsy specimens were obtained from muscles supplied by branches of the brachio-cervical essels and 10 from leg muscles.

CLASSIFICATION OF HISTOLOGICAL ARTERIAL CHANGES

I previous publication (Hamrin, Jonsson & Landberg 1964) the histological arterial changes were divided into 3 groups.

1 *Sclerosis of the blood essels* with some degree of intimal thickening and calcification in the media without any inflammatory changes. This sclerosis was seen in almost all excised arteries.

2. *Non-specific arteritic changes.* — The blood-vessel wall showed an inflammatory exudate, predominantly of lymphocytes but also of plasma cells and macrophages. I the mildest cases the exudate was confined to the adventitia only or to the outer parts of the media, but in severe cases inflammation affected the whole wall of the artery N fibrinoid necrosis was seen. The adventitia often showed a marked fibrotic thickening.

3 *Giant-cell arteritis* mostly with an intense inflammatory reaction and an admixture of multinucleated giant cells and sometimes small fibrinoid ne-

croses. The arteritis was often combined with sclerosis of the vessel walls, and in some cases a giant-cell reaction was seen around small calcifications in the media.

This classification of the histological arterial changes was retained throughout the investigation All of the pathologist's reports thus contained information as to whether inflammatory changes had been observed or not, and if so, whether multinucleated cells had been demonstrated In a later publication the term non specific was altered to uncharacteristic (Hamrin, Jonsson & Hellsten 1968) in order to avoid giving the impression that giant cells are specific of this form of arteritis which, judging from the literature on the pathology referred to in Chapter 2, is not the case In the description of the microscopic findings the specimens of the arteries are however divided into giant-cell arteritis and uncharacteristic arteritis It should be mentioned that fibrinoid necrosis was observed also in the absence of giant cells. When the above classification was considered of less interest, the term positi e biopsy or only arteritis is used to designate inflammatory changes in a biopsy specimen whether giant cells had been demonstrated or not In the absence of inflammatory changes the biopsy specimen is described as negati e, even though sclerotic changes were nearly always demonstrable Sometimes sclerotic changes and other changes suggesting previous arteritis were seen in the arterial wall, but such changes were not classified here as arteritis. The occurrence of active inflammatory changes in the vessel wall was considered obligatory for a histological diagnosis of arteritis. Attempts were thus not made to distinguish post arteritic from degenerative arterial changes even though certain pathologists feel that such differentiation is possible to do (Ainsworth et al 1961)

BIOPSY FINDINGS

Biops specimens of the temporal artery were obt ined on one or both sides in 84 (90) of the 93 cases of PMA It is clear from Table 7 that in 48 (57) of the biopsied cases arteritis was demonstrated while biops was negative in 36 (43) In two thirds of the positive cases giant-cell arteri wa demonstrated and in one third uncharacteristic arteritis

The sex distribution f the patients in whom biops wa posit e w s eq l (T ble 7) But the n mber of men from whom bi ps pecimens were obt ined wa smaller than th t women The

Histological findings in temporal arteries	Number of cases Males	Females	Total
Giant-cell arteritis	19	14	33
Uncharacteristic arteritis	5	10	15
No arteritis	1	24	36
Total	36	48	84

Table 7 Microscopical appearance of temporal arteries in 84 biopsied cases of PMA.

percentage of positive biopsies among men was therefore higher (67 /) than among women (50) This difference was not significant

In 12 of the above 84 patients the temporal region was explored bilaterally at an interval of 1—20 months between the sides (Table 8) The first biopsy was done equally often on the right side as on the left In 3 cases no representative material was obtained at the first operation, but the specimen obtained at the second showed arteritis. In 7 of the 1 cases in which biopsy was repeated, biopsy on the first occasion had proved negative In 3 of these cases repeated biopsy showed microscopic arteritis in the contralateral artery while in 3 other cases, also repeated biopsy was negative In 1 of the 7 cases with a negative biopsy on the first occasion, exploration on the second occasion 0 months later produced no representat ve vessels. This was in case 65 which was also commented upon in the account of the biopsy material

In 2 cases (Nos 5 and 18) arteritic lesions were found in both temporal arteries, from which biopsy specimens were obtained at an interval of 4 and 15 months, respectively In case 5 the f st biopsy specimen showed giant-cell arteritis and the second uncharacteristic arteritis, and in case 18 it was the other way round. In case 18 the first biopsy was done within the first month of the disease

Of the cases explored bilaterally then the first biopsy revealed arteritis in 2 of the 1 cases, and the second exploration 1—16 months later revealed arteritis in 6 of the remaining 10

Interval between clinical onset of disease and biopsy of the temporal artery

The time of onset was uncertain in 1 of the 48 cases in which biopsy specimens were posit ve In the remaining 47 positive cases the interval between onset of disease and [illegible] of the temporal artery

Case No.	Temporal symptoms and signs[1])	Results[2]) of histological examination at		Interval in months between			
				onset of PMA and			
		first biopsy	second biopsy	clinical TA[3])	first biopsy	second biopsy	first and second biopsy
2	(★)	0	+	64	68	73	5
5	0	GCA	+	—	6	10	4
18	★	+	GCA	0	0	15	15
28	(★)	0	0	8	3	10	7
32	0	0	+	—	4	9	5
38	(★)	—	+	(—9)	4	8	4
40	(★)	0	+	17		18	16
59	0	—	+	—	8	17	9
65	0	0	—	—	31	51	20
72	(★)	0	0	4	5	19	14
76	(★)	0	0	2	5	21	16
82	0	—	+	—	3	4	1

Table 8 Results of biopsies of temporal arteries on both sides in 12 cases of PMA.

[1]) For explanation see Table 6.

[2]) GCA means giant-cell arteritis, + uncharacteristic arteritis, 0 no arteritis and — no representative artery at exploration.

[3]) In case No. 38 vague clinical symptoms occurred 9 months before onset of myalgic symptoms.

ranged from 0—20 months in 45 cases and was more than 2 years in .. In the 36 negative cases the interval was 0—21 months in 31 cases and more than 2 years in the remaining cases. Mean interval ± SD for the interval between onset of disease and biopsy in the 47 positive cases was 9.6 ± 11 16 months and in the 36 negative cases 11 4 ± 12.50 Using the t-test there was no significant difference between positive and negative cases.

Table 9 Histological findings in 84 cases of PMA grouped according to steroid therapy at time of biopsy

Microscopical appearance of temporal artery at biopsy	Steroid therapy at time of biopsy			No. of cases
	Not given	Ended	In progress	
Arteritis	33	10	5	48 (57 %)
No arteritis	24	9	3	36 (43 %)
Total	57 (68 %)	19 (23 %)	8 (9 %)	84 (100 %)

Results of biopsies in relation to steroid therapy

57 (67.9 %) of the 84 biopsied patients had not received any steroid therapy before biopsy (Table 9) In 19 (22.6 %) of the cases biopsy was done after treatment with prednisolone and in 15 of these the prednisolone cure had been concluded more than 4 weeks before biopsy and in 8 (9.5 %) biopsy was obtained during treatment with steroids. In 7 of these 8 cases the prednisolone dose was 15 mg or less per day at the time of biopsy In the 8 cases in which representative biopsy specimens were obtained from the temporal arteries on both sides, only the first positive biopsy specimens are included here and, when both were negative, the second one.

Table 9 shows that positive biopsy specimens were obtained in 33 (57.9 %) of the 57 cases not treated with steroids and in 15 (55.6 %) of the 27 cases receiving steroids or who had received steroid therapy earlier in their disease. The difference in the results of biopsy between these groups was thus little and not statistically significant.

CASE NO.	NUMBER OF ARTERIES RESECTED	EXTRATEMPORAL ARTERIES RESECTED: OCCIPITAL	CIRCUMFLEX SCAPULAR	SUPERIOR GLUTEAL	SECOND PERFORATING BR. OF FEMORAL ARTERY
		2 CASES	6 CASES	2 CASES	6 CASES
1	2			POS	POS
3	2	POS	NEG		
4	2		NEG		NEG
6	1		NEG		
7	1				NEG
[illegible]	1		NEG		
[illegible]	1				NEG
[illegible]	1		NEG		
21	1				NEG
22			NEG		
49	2			NEG	POS
64	1	POS			

T ble 10 Results of biopsies of extratemporal arteries in 12 cases of PMA. Signs of uncharacteristic arteritis found i some of the essels in 4 cases.

Extratemporal arteries

Table 10 summarises the histological findings at biopsy of 16 arteries other than the temporal arteries from 12 patients. Biopsy of the temporal artery was positi e in all of these cases except Nos 21 and 22 In 4 cases with a positive biopsy of the temporal artery arteritis was also found in 5 of the extratemporal arteries

Findings in other biopsy specimens

Concomitant veins, examined microscopically in 5 cases showed no changes The segment from the thrombotised subcutaneous vein in case 67 showed only an organised thrombotic mass, while the vein wall showed no inflammatory changes

Microscopic examination of 18 muscle specimens from 15 patients showed no noteworthy pathologic changes

DISCUSSION

In suspected PMA arterial biopsy appears justified because it may verify the suspicion in more than h lf of the cases If biopsy is to be satisfactory it should be performed at the proper time and, second, by a surgeon w th experience of such operation The commonest sign of arteritis at operat on w the presence of periarterial adhesions. These were somet mes so extensive that the vessel and it surroundings h d the ch racter of scarred ind r ted tissue from w h the rtery had to be [illegible] sed In such [illegible] p tients had probably had inflammat on [illegible] me The temporal arteries in these cases p [illegible] on racted, they were sometimes ext em l [illegible] d hed onl scan [illegible]

Knowledge of the disseminated nature of the inflammation is also important. If that part of the *artery first encountered appears normal, it might* be rewarding to extend the incision and continue the search. This may be exemplified by case 70 in the present material A piece of the frontal branch was excised first in this case, but as the exposed branch appeared normal, the incision was extended down to the bifurcation of the temporal artery where the vessel appeared changed. A piece of the trunc and of the bifurcation was also excised The piece excised first proved, not unexpectedly to be free from inflammatory changes, while the segment excised last was microscopically the site of giant-cell arteritis With increasing experience it was possible at biopsy to some extent to predict the results of microscopic examination In at least a few cases, however there was no distinct inflammation at histological examination though the vessel was so adherent to an indurated tissue that dissection was difficult.

At the Mayo-clinic (Birkhead et al 1957) the freezing technique was described as useful in the search during operation of an affected portion of the artery These authors also recommend repeated biopsy if temporal arteritis was strongly suspected. The value of repeated biopsy is apparent from our experience where arteritis was *not diagnosed* before the second exploration in 6 of 10 cases.

Because of the focal nature of the arteritis a negative biopsy does not exclude giant-cell arteritis (Harrison 1948 Palm 1958 Paulley & Hughes 1960). Microscopically inflammatory infiltration or granuloma may be encountered in a short segment of an artery while adjacent parts may be free from the inflammatory cells The segmental character of the arteritic changes appears to show up well at angiography of the temporal artery (Gillanders et al 1969) This might explain why biopsy may sometimes be negative in clinically strongly suspected cases of temporal arteritis (Palm 1958 Kahn 1966), and probably also explain the negative biopsy in our case No 78 with clinically strongly suspected symptoms of temporal arteritis

Biopsy of extra-temporal arteries has been recommended and performed in a few cases of temporal arteritis In a compilation of 249 cases of temporal arteritis Roux (1954) reported positive findings at biopsy of the occipital artery in some cases and of a foot artery in 7 cases, and in 1 case from a facial artery and from branches of the thy

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Comparison between the results of biopsy in cases without and with steroid therapy suggests that steroid therapy in the relatively small doses given do not affect the inflammatory tissue reaction so strongly as to make itself felt in the present material. These doses are, however evidently capable of having a favourable effect on both local and systemic symptoms of the disease

In 14 representative series of polymyalgia syndrome (Kersley 1951 Gordon 1960, Boyle & Beatty 1961 Carlander 1961 Serre & Simon 1963 Bagratuni 1963 Berg & Lange 1963 Olhagen 1963 Weissenbach et al. 1963 Gordon et al. 1964 Kogstad 1965 de Sèze et al. 1965 Wilske & Healey 1967 Bruk 1967) muscle biopsy was performed in 90 cases. In 6 of these mild and probably insignificant changes were found The negative biopsies in our series agree with these experiences.

Thus, histological examination of muscle biopsy specimens with routine histological methods appears to be of no diagnostic value.

In his critical examination of the literature on temporal arteritis Harrison (1948) stated that it appears less likely that the veins are appreciably attacked in the disease, because if they were, it would surely have been noticed, but nevertheless he states that a systemic examination of the veins would be useful. No such investigation appears to have been published. A few observations have been reported which can probably be explained by extension per continuitatem of the inflammatory process of an artery to the concomitant vein (Cooke et al. 1946, Crosby & Wadsworth 1948). This is probably exemplified by our case 68 in which a subcutaneous, hard thrombotised vein, not tender to palpation, could be followed from the back of the hand to the axillary fossa. The absence of microscopic inflammatory changes in the wall of the vein and in other vein biopsies in this series agrees with Harrison's opinion Also on exposure of the temporal artery we found that the concomitant temporal veins were never involved by the inflammatory process, as judged from the gross findings at surgical exploration.

EXTRA-TEMPORAL ARTERIES RESECTED

CASE NO.	NUMBER OF ARTERIES RESECTED	OCCIPITAL	CIRCUMFLEX SCAPULAR	SUPERIOR GLUTEAL	SECOND PERFORATING FROM FEMORAL ARTERY
		2 CASES	CASES	2 CASES	8 CASES
1	2			POS	POS
3	2	POS	NEG		
	2		NEG		NEG
	1		NEG.		
					NEG
[illegible]			NEG		
[illegible]					NEG
[illegible]	1		NEG.		
21	1				NEG
22	1		NEG.		
[illegible]	2			NEG.	POS.
64	1	POS			

Table 10. Results of biopsies of extratemporal arteries in 12 cases of PMA. Signs of uncharacteristic arteritis found i some of the vessels in 4 cases.

Extratemporal arteries

Table 10 summarises the histological findings at biopsy of 16 arteries other than the temporal artery from 12 patients. Biopsy of the temporal artery was positive in all of these cases except Nos 21 and 22. In 4 cases with a positive biopsy of the temporal artery arteritis was also found in 5 of the extratemporal arteries.

Findings in other biopsy specimens

Concomitant veins, examined microscopically in 5 cases showed no changes The segment from the thrombotised, subcutaneous vein in case 67 showed only an organised thrombotic mass, while the vein wall showed no inflammatory changes.

Microscopic examination of 18 muscle specimens from 15 patients showed no noteworthy pathologic changes

DISCUSSION

In suspected PMA arterial biopsy appears justified because it may verify the suspicion in more than half of the cases If biopsy is to be satisfactory it should be performed at the proper time and, second, by a surgeon with experience of such operations The commonest sign of arteritis at operations was the presence of periarterial adhesions. These were sometimes so extensive that the vessel and its surroundings had the character of a scarred indurated tissue from which the artery had to be excised. In such cases the patients had probably had inflammation for long time The temporal arteries in these cases ppe red contracted, they were sometimes ext emely th and bled only scantily or not t ll on incision

Knowledge of the disseminated nature of the inflammation is also important. If that part of the artery first encountered appears normal it might be rewarding to extend the incision and continue the search. This may be exemplified by case 70 in the present material. A piece of the frontal branch was excised first in this case, but as the exposed branch appeared normal, the incision was extended down to the bifurcation of the temporal artery where the vessel appeared changed. A piece of the trunc and of the bifurcation was also excised The piece excised first proved, not unexpectedly to be free from inflammatory changes, while the segment excised last was microscopically the site of giant-cell arteritis. With increasing experience it was possible at biopsy to some extent to predict the results of microscopic examination In at least a few cases, however there was no distinct inflammation at histological examination though the vessel was so adherent to an indurated tissue that dissection was difficult.

At the Mayo-clinic (Birkhead et al 1957) the freezing technique was described as useful in the search during operation of an affected portion of the artery These authors also recommend repeated biopsy if temporal arteritis was strongly suspected The value of repeated biopsy is apparent from our experience, where arteritis was not diagnosed before the second exploration in 6 of 10 cases.

Because of the focal nature of the arteritis a negative biopsy does not exclude giant-cell arteritis (Harrison 1948 Palm 1958 Paulley & Hughes 1960). Microscopically inflammatory infiltration or granuloma may be encountered in a short segment of an artery while adjacent parts may be free from the inflammatory cells. The segmental character of the arteritic changes appears to show up well at angiography of the temporal artery (Olllanders et al. 1969) This might explain why biopsy may sometimes be negative in clinically strongly suspected cases of temporal arteritis (Palm 1958 Kahn 1966), and probably also explain the negative biopsy in our case No 78 with clinically strongly suspected symptoms of temporal arteritis.

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13			NEG.		
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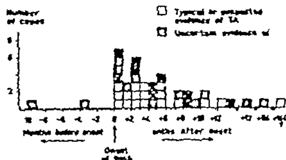


Fig. 4 Interval between onset of PMA and of clinical symptoms of temporal arteritis (TA). × denotes clinically diagnosed but not histologically verified, cases of PMA.

that the yield of the diagnostic biopsy was much greater in the former group than in the latter and that this difference was highly significant (chi-2 = 11.88, DF = 1 p <0.001). It is, however noteworthy that 18 (41 %) of the 44 patients who had no symptoms in the temporal area showed inflammatory signs of temporal arteritis.

INTERVAL BETWEEN ONSET OF PMA AND CLINICAL SYMPTOMS OF TA

Including cases with only vague symptoms of TA, 40 (48 %) of the 84 from whom biopsy specimens were obtained had evidence of previous or existing TA. Fig. 4 gives the interval between the onset of PMA and clinical symptoms of TA in these 40 cases. In 10 of the cases biopsy specimens of the artery showed no signs of inflammation, while arteritis was verified in the remaining 30 cases. Of these 30 patients 2 had had transient symptoms in the temporal area 9 and 3 months, respectively before the onset of PMA. In 5 cases the symptoms of TA appeared during the first month of the disease. In 19 local temporal symptoms occurred during the first half year of PMA and in 5 during the second half year. In 2 cases symptoms of TA appeared during the second year of the disease. One of these cases (No 15) was mentioned in Chapter 4. Finally clinical evidence of TA appeared in cases several year after the onset of the basic disease. In one of these two cases the local temporal symptoms were doubtful (case No 2) and in the other (No 34) with a clinically classical TA the onset of polymyalgia was uncertain.

EYE SYMPTOMS

All patients with known visual disturbances and many but not all, of the others were examined opthalmologically at least once.

Ocular symptoms were found only among patients with histologically verified arteritis. Of these, 4 had diplopia and in . of them (Nos 7 and 81) diplopia was the only eye symptom, while in the other two (Nos 6 and 34) the diplopia had been followed by impairment of vision.

Two of the patients had permanent amaurosis. One (No 6) lost vision of both eyes within about . days 6 weeks after the onset of PMA. He was at that time receiving 1. mg triamcinolone a day which dose could thus not prevent amaurosis. In the other case (No 29) the patient lost vision on the right side after 7 months' rheumatic disease. He had been blind on one eye for about a week and had not received steroids, when he was admitted to the eye department. Steroid therapy had no effect on amaurosis, but the other eye was not affected. This 71-year-old man was worried more about pain in the neck and shoulders than loss of vision.

Patient No 34 had noticed progressive impairment of vision of the right eye for about a day when she was admitted to the eye department. She could barely discern hand movements with the right eye while vision of the left eye was 1.0. She had not received steroids and immediately after admission she was given 60 mg prednisolone a day and heparin. Vision improved considerably the first day and after a few days vision on the right side was as high as 0.7. One year previously it had been 1.0 also on the right side.

In two sisters (Nos 54 and 77) flittering scotoma and amaurosis fugax, respectively occurred without later permanent impairment of vision. The cases are described further in Chapter 8.

The treatment and prognosis of eye complications are dealt with in association with the discussion of the Malmö series of temporal arteritis (Chapter 1?).

COMMENTS

Almost half of the patients thus had symptoms or signs in the temporal region. This might lea e the impression that the patients had been selected large

HISTOLOGICAL AND CLINICAL RELATION BETWEEN POLYMYALGIA ARTERITICA AND TEMPORAL ARTERITIS

LOCAL SYMPTOMS AND SIGNS IN THE TEMPORAL AREA

The patients were divided into the following four groups according to symptoms and signs in the temporal area

Group with classical clinical picture of temporal arteritis (TA). To this group were assigned clinically classical cases with reddening, swelling and tenderness along the temporal arteries, and were cases with amaurosis or visual impairment even in the absence of any of the classical signs of inflammation

Group with cases with suspect symptoms of TA in the history and/or at physical examination. Here suspect anamnestic symptoms are to be understood as symptoms — reported by the patient himself or some relative or person looking after the patient — swelling, tenderness or pain in the temporal area. Patients with reported swollen or cord-like arteries in the temporal area were also assigned to this group. The group also included cases in which anamnestic data were less distinct but in which the examination of the temporal arteries had revealed suspect signs: mild tenderness along the vessels, nodularity of arteries and uncertain or weak pulsations in the temporal arteries, especially if the strength of the pulse on one side was different from that on the other

Group with only vague memory of any symptom in temporal region. In these cases clinical examination of the temporal arteries revealed nothing abnormal. As a rule it was not until after repeated questioning that information was obtained about mild and transient symptoms in the temporal region described as ear-ache or pain in the mandibular joints when chewing. In these cases the answers were sometimes such that a suggestive effect at repeated taking of the history could not be excluded

Group with no symptoms or signs of TA

During the relatively long period covered by the collection of the present material, the author had presumably improved his skill in the discovery and evaluation of symptoms and signs of TA. Attempts were nevertheless made to adhere to the above-mentioned gradation of clinical signs of TA.

It is clear from Table 11 that 17 (21) of the 84 patients from whom biopsy specimens were obtained of the temporal artery had typical or suspect symptoms and signs of TA and 67 (79) had only mild or no symptoms in the temporal region in their history. If however patients with only uncertain symptoms of TA in their history be included, it would mean that 40 (48) had clinical symptoms or signs of TA. But in 44 (5?) no symptoms at all in the temporal area appeared during the observation period

Table 11 also shows that the clearer the clinical signs of temporal arteritis the better the prospects of demonstrating inflammatory changes in the artery in biopsy specimens. Thus, arteritis was demonstrated histologically in 16 (94 %) of the 17 patients with classical or suspect symptoms and signs of TA, compared with only 3 (48) of the 67 with uncertain or no symptoms of TA. On comparison of these larger groups it was found

Table 11. Clinical symptoms and signs of temporal arteritis (TA) related to results of biopsy of temporal artery in 84 cases of PMA.

Microscopic appearance of temporal arteries	Temporal symptoms and signs: Clinically classical TA	Suspected symptoms and/or signs of TA	Uncertain symptoms of TA. No signs	No symptoms or signs of TA	
Arteritis	4	1	14	18	48 (57)
No arteritis	0	1	9	6	36 (43)
Total	4 (5	13 (16 %)	-3 (27)	44 (52)	84 (100)

Table 1. Survey of published series of PMA with systematic or frequent biopsy. Parts of present series published previously denoted by italics. TA = temporal arteritis.

Cases of		No of cases	Men Women	No of cases with biopsied arteries	f % cases	arteritis at biopsy	of biopsied cases	Diagnostic principle and selection of patients for biopsy
Alestig & Barr	1963	10	5 5	9	90	7	78	Clinical picture of TA. Systematic biopsies.
Skånet	1963	47	16 31	47	100	31	66	Rheumatic symptoms more common than symptoms of TA. Age 60—80 years in most cases. E. S. R. 100 mm in 30 cases.
Hamrin et al	1964	23	14 9	21	91	16	76	Definite diagnostic criteria for PMA. Systematic biopsies.
Hamrin et al	1965	52	3 29	48	92	29	60	See above.
Kogstad	1965	70	24 46	16	23	12	75	Clinical pictur f PMA. All patients biopsied had headache and 10 also "temporal signs.
Dixon et al	1966	31	5 26	31	100	13	4	All cases ith symptoms of PMA or TA biopsied. E. S. R. >40 mm.
Hamrin	1966	58	27 31	54	93	33	61	See above.
Bruk	1967	80	19 61	33	41	15	45	Special diagnostic criteria. Raised E. S. R. not an absolute requirement but 68 had E. S. R. >100 mm. Temporal artery biopsied in 31 cases, occipital artery in and facial artery in ..
Larsson	1968	11	3 8	11	100	8	73	Clinical pictur of PMA. One of the patients had a typical clinical picture of TA.
Hunder et al	1969	80	—	27	34	8	1	Clinical picture as in PMA. 5 of the biopsied cases had clinical signs of arteritis.
Hamrin	1971	93	39 54	84	90	48	57	See above.
		422		58	62	14	55	

Microscopic examination of arteries	No of cases with demonstrated arteritis	No of cases without demonstrated arteritis	Total
Biopsy only	41	33	74
Post mortem only		0	2
Both biopsy and post mortem	8		10
Not performed	—	7	7
Total	51	4	93

Table 13 Microscopic findings in biopsy and necropsy specimens of arteries in 86 of 93 cases of PMA.

1 In 1 of these 8 cases arteritic changes were found only in biopsy tissue and in 1 only in necropsy tissue while in the remaining 6 inflammatory changes were seen in biopsy specimens and necropsy specimens of the temporal artery and large arteries.

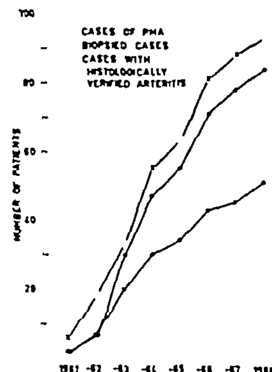


Fig 6 Cumulative curves for 93 cases of PMA according to annual number of diagnosed cases, number of cases with histologically examined arteries and cases with positive histological findings.

biopsy specimens of the temporal artery obtained during the same year and as previously described, inflammatory changes were seen in the vessels in all of them. During 1963 biopsy specimens were obtained from a further ... cases, namely in 9 that had been diagnosed th ... e ... and in 14 of the 15 diagnosed in 1963. During the first 3 years 33 cases were diagnosed and in 30 of them biopsy specimens were obtained of the temporal artery. In 0 of these 30 cases arteritis was demonstrated. In 3 (Nos 8, 20 and 49) of the cases diagnosed in the first 3 years no biopsy specimens were obtained during those years or later. During the following years a further 6 cases were diagnosed in which no biopsy specimens were obtained, namely two (Nos 41 and 90) in 1964, two (Nos 69 and 74) in 1966, one (No 80) in 1967 and one (No 91) in 1968. The reasons why no biopsy specimens were obtained in these cases have been given previously (Chapter 4).

SEX AND AGE DISTRIBUTION OF HISTOLOGICAL CHANGES

Arterial tissue was examined in 37 of the 39 males and in 49 of the 54 females. Arteritic changes were demonstrated in 25 (68) of the males examined and in 6 (53) of the females. The difference in frequency of positive findings with sex was not significant. Fig 7 gives the age and sex distribution of the histological findings. Of the 69 patients above 65 years, the arteries were examined histologically in 64. Arteritic lesions were observed in 45 (70) of these 64 cases. In 6 (27) of the subjects below 65 and examined histologically arteritis was diagnosed patho-anatomically. The frequency of arteritis demonstrated histologically was thus more common in patients above 65 years. The difference was highly significant (chi = 1 .57 DF 1 p <0.001)

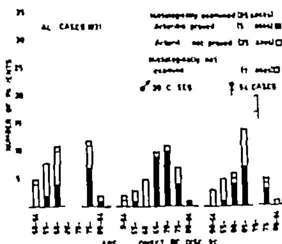


Fig 7 Frequency distribution of histological findings in 93 cases of PMA.

CHAPTER 7

CLINICAL ANALYSIS OF POLYMYALGIA ARTERITICA

In the following account and analysis of the Växjö series the 93 cases were divided into series A and B Series A consisted of the 51 cases which, as mentioned in the previous chapter had histologically verified arteritis. Series B consisted of the remaining 42 cases Microscopic examination had revealed no inflammation in available specimens of the arteries in 35 and in the remaining 7 no such examination was performed.

ERYTHROCYTE SEDIMENTATION RATE

One (case 77) of the patients did not fill one of the obligatory diagnostic criteria, *viz.* an E. S. R. of more than 50 mm/1 hr In that case the E. S. R. was, however measured on only one occasion before institution of steroid therapy The highest individual E. S R levels recorded in the entire material varied between 47 and 155 mm/1 hr (Fig 8) Table 14 gives the mean maximal E. S R. for the entire material, for series A, for series B and for each sex in both series. These means were very similar for both sexes in series A and fo females in series B, while that for men in series B was lower

Comments

Even in the first reports of PMA raised E. S. R. was described as characteristic of the disease (Meulengracht 1945 Meulengra ht & Schwartz 195_ and Holst & Johansen 1945). Porsman (1951) wrote that "the most astonishing thing was the very high sedimentation rate, which was often on 100 and above In Bagratuni's (1956) material the mean of the highest E. S. R. values was 100 mm (Table 3) In a compilation of various series (Serre et al. 1962) the mean in 6 of these series ranged between 49 and 81 mm and in a 7th series it was 110 mm

In two series, published in the 60s and including cases of histologically verified arteritis, the mean f the highest E. S. R. was 100 mm (Alestig & Barr 1963) and 102 mm (Wilske & Healey 1967), respectively In an ophthalmological series consisting of 31 cases of temporal arteritis with severe visual

Series	No in series	Mean values of ESR	SD
A+B	93	103	26.5
A	51 (34)	106 (105)	27.5 (25.5)
A males	25 (15)	108 (100)	26.2 (24 4)
A females	6 (19)	105 (108)	29 0 (26.4)
B	42	99	25 0
B males	14	86	20 1
B females	28	106	25.0

Table 14 Highest E. S. R. (mm/1 hr) (Westergren) in 93 cases f PMA, diagnosed at the department f internal medicine in Växjö between 1961 and 1968. I brackets, corresponding values in 34 cases of histologically erified arteritis admitted to the department of internal medicine in Malmö between 195 and 1962 (Chapter 12).

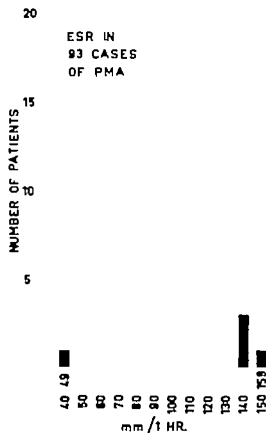


Fig. 8 Highest E. S. R. (Westergren) recorded in 93 cases of PMA. Mean ± S. D = 103 ± 26.5 mm/1 hr

impa rment the mean of the highest E S R v lues was 96 mm with a range of 50—145 mm (Palm 1958) In the present series of PMA the corres ponding mean f und for the 93 cases was 103 mm, and for the 51 erified cases, 106 mm (range 47—155 mm)

The range of variation of the E S R thus varied widely from one series to another prob bly w th the diagnostic criteria used In some series a raised E. S R was not considered obligatory for the diagnosis In one series of 51 cases, f r example the E S R was normal in 4 (Wersenb ch et al 1963) and in another consisting of 80 cases, the E. S R was less than 0 mm/1 hr in 13 of the patient (Bruk 1967) This last mentioned material included 2 cases with histologically er fied arte ritis, in which the highest E. S. R recorded had been 20 mm 1 hr Bruk also reported that he had seen a patient with histologically verified arteritis and impaired sion with an E. S R as low as 8 mm/1 hr two weeks before visual impairment had occurred These observations should be borne in mind A normal or sl ghtly raised E S R is thus compatible with a histologically verifiable arteritis In 10 of the histologically verified cases of arteritis in the present series E S R before steroid the rapy was less than 50 mm/1 hr at the time of biopsy and in 5 of these patient it ranged from 15 to 30 mm Also post-mortem examination suggested that a mild inflammation of the arterial walls may per sist for years after the acute phase of the disease Thus, the finding of arteritis in a biopsy specimen from a p tient with only slightly raised or even normal E S R. need not argue against the fact the E. S R being raised and usually markedly raised during the clinically active phase of the di sease It is poss ble that the rise in E. S R varies not only with the intensity of the inflammation, but also with its spread among vessels less read ly accessible to clinical diagnosis. This is supported by the fact that at post mortem the aorta nearly always (Chapter 1) seems to be the site of inflamma tory changes and that in the present series those patients who developed an aortic arch syndrome had a remarkably high E S R (Chapter 10)

In Scandina ia me surement of the E. S. R. by the method of Westergren has for several decades been used as a clinically aluable screening me thod It often happens that patients are referred to the department of internal medicine for in est ga tion of a high E. S R., for which no explanation is initially available In such cases myeloma and re nal cancer are often first suspected In our first publicat on (Hamrin et al 1964) we therefore compared the first 3 cases with clinically diagnosed cases of renal cancer and myeloma seen during the same period with respect to E. S R It so happened that the number of the last two diseases taken together w the same as that of PMA In the group with myeloma and renal cancer the E. S R in 8 was above and in 15 cases below 100 mm/1 hr wh le in the PMA series the E S R was above in 15 cases and below 100 mm in 8

Judging from extensive personal experience it would appear that in middle aged and elderly per sons with a high, obscure E. S R PMA should be *one of the f rst diseases to be suspected*

In several cases in the present material the find ing of a high E. S R. was a surprise to the examiner and often induced him to refer the patient to hos pital for immediate in estigation

The increase in E. S R is not always proportional to the rheumatic ymptoms. PMA with fever with a very high E. S R in a patient with a very poor general condition may persist for one or se veral months before any rheumatic symptoms ap pe r (see below) Such cases are then regarded as in tances of fever of unknown origin or suspected malignancy with a markedly increased E. S R. In one case in the present material in which the patient had histologically verified arteritis and aortic arch syndrome and had been ill for 1 year (case 93) the rheumatic symptoms were so mild and appeared so late in the course of the disease that the case only w th doubt satisfied the criteria set up The general symptoms, on the other hand, were con siderable with longstanding fever an E. S R. with a maximum of 135 mm/1 hr and considerable loss of weight. There are probably cases of PMA which even after long observation develop practically no rheumatic symptoms and for which the term poly myalgia is inadequate

RHEUMATIC SYMPTOMS AND SIGNS

Mode of onset of disease

The cases were classified according to the character of the onset as acute or subacute Here acute is to be understood as a fairly rapid onset, which the patient could date while subacute is to be under stood as a more insidious onset

In case 34 the patient had been ill for about 12

years before diagnosis, and the character of the onset could not be judged which, however appeared possible in the remaining 92 cases. In 37 (40 %) of these patients the onset was acute and in 55 (60 %) it was subacute. No significant difference in type of onset was demonstrable between series A and B or between males and females

An acute onset usually resembles that of influenza with fever diffuse widespread migrating myalgia but without catarrhal symptoms. In some cases, however the patients reported painful swallowing, which occasionally occurred also later in the course of the disease, and in some cases the doctor who examined the patient first had diagnosed pharyngitis or angina tonsillaris. The patients the author examined while they still had swallowing discomfort were tender to palpation along the carotids, and no signs of pharyngitis could be observed. The possibility that such symptoms may be due to inflammation of the carotid arteries has been pointed out earlier (Paviot et al. 1934 Lindquist 1948 Strachan 1966) and appears plausible.

When the onset was subacute, general symptoms usually appeared at roughly the same time as the rheumatic symptoms, but in some cases the rheumatic symptoms were preceded by prodromal stage characterised by fatigue, loss of appetite loss of body weight, fever and sweating.

In some of the cases the rheumatic symptoms were already initially intense and accompanied by stiffness of the cervical spine shoulders and/or hips during the initial stage, *i.e.* the first week of the disease In other cases the myalgia appeared successively and stiffness of neighbouring joints did not appear until after one or more weeks, sometimes not until after months. In 4 cases (Nos 22, 82, 92 and 93) no rheumatic symptoms occurred in the initial stage, but not until after a long prodromal stage of 1 5—11 months. Patients Nos 41 and 43 who had a long history could not remember what the symptoms were like at onset. In 91 cases, however information was available about the severity and the occurrence of rheumatic symptoms in the initial stage Table 15 shows that an insidious onset of the rheumatic symptoms was more common than an acute onset.

Primary localisation of myalgia

The earliest rheumatic symptoms had the character of myalgia and the patients could usually define the site of the symptoms. In Table 16 the patients are distributed among 4 main groups according to the primary localisation of the myalgia The first two main groups which comprised 89 (96 %) of the patients, included cases with a brachio-cervical or caudal localisation of the myalgia. There were 59 (63 %) patients with myalgia initially confined to the brachio-cervical groups of muscles and 30 (32 %) with a caudal localisation

Rheumatic manifestations at onset of disease	Series A			Series B		
	M	F	M+F	M	F	M+F
Impairment of joint mobility	10	8	18	3	14	17
Only myalgia	14	15	29	10	13	23
Not present	1	2	3	1	0	1
	25	25	50	14	27	41

Table 15 91 of 93 cases of PMA distributed according to rheumatic manifestations at onset of disease, *i.e.* the first week of disease.

Primarily affected muscle groups	Number of cases
Brachio-cervical region	
Back of the neck	22
Shoulders	25
Back of the neck and shoulders	10
Upper arms	2
	59
Caudal region	
Hips and gluteal regions	18
Thighs	10
Calves	2
	30
Brachio-cervical and caudal regions	
Shoulders and hips	
	2
Other localisations	
Back	1
Diffuse distribution	1
	2
Total	93

Table 16. The initial localisation of muscle pain in 93 cases of PMA.

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The increase in E. S R. is not always proportional to the rheumatic symptoms PMA with fever with a very high E. S R. in a patient with a very poor general condition may persist for one or several months before any rheumatic symptoms appear (see below) Such cases are then regarded as instances of fever of unknown origin or suspected malignancy with a markedly increased E. S R. In one case in the present material in which the patient had histologically verified arteritis and aortic arch syndrome and had been ill for 1 year (case 93) the rheumatic symptoms were so mild and appeared so late in the course of the disease that the case only with doubt satisfied the criteria set up The general symptoms, on the other hand, were considerable with longstanding fever an E. S. R. with a maximum of 135 mm/1 hr and considerable loss of weight. There are probably cases of PMA which even after long observation develop practically no rheumatic symptoms and for which the term polymyalgia is inadequate.

RHEUMATIC SYMPTOMS AND SIGNS

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In some of the cases the rheumatic symptoms were already initially intense and accompanied by stiffness of the cervical spine, shoulders and/or hips during the initial stage, the first week of the disease. In other cases the myalgia appeared successively and stiffness of neighbouring joints did not appear until after one or more weeks, sometimes not until after months. In 4 cases (Nos 22, 82, 92 and 93) no rheumatic symptoms occurred in the initial stage, but not until after a long prodromal stage of 1.5—11 months. Patients Nos 41 and 43, who had a long history, could not remember what the symptoms were like at onset. In 91 cases, however, information was available about the severity and the occurrence of rheumatic symptoms in the initial stage. Table 15 shows that an insidious onset of the rheumatic symptoms was more common than an acute onset.

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Table 15. 91 of 93 cases of PMA distributed according to rheumatic manifestations at onset of disease i.e. the first week of disease.

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Brachio-cervical region	
Back of the neck	22
Shoulders	25
Back of the neck and shoulders	10
Upper arms	2
	59
Caudal region	
Hips and gluteal regions	18
Thighs	10
Calves	2
	30
Brachio-cervical and caudal regions	
Shoulders and hips	2
	2
Other localisations	
Back	1
Diffuse distribution	1
	2
Total	93

Table 16. The initial localisation of muscle pain in 93 cases of PMA.

On comparison between series A and B regarding the frequency of cases with primary localisation of the myalgia to the brachio-cervical muscles it was found that this localisation was somewhat more common in series A than in series B. The difference was, however, small and not statistically significant.

Clinically involved muscle groups

The myalgia showed a marked tendency to migrate with successive involvement of new muscle groups, sometimes gradually, sometimes suddenly. In both cases this generally occurred during the first 3—4 months of the disease but sometimes later. When the interval was long the regions initially attacked had sometimes recovered and the longer such an interval the more the symptoms assumed the character of an exacerbation rather than progression of the disease. In the same way as in a previous paper (Hamrin et al. 1964), Table 17 gives the topographical distribution of the myalgic symptoms in the systematically examined muscles in the back of the neck, shoulders, upper arms, in the pelvic girdle and in the muscles of the thigh. The table covers the entire period of observation in all the 93 patients who were divided among 10 groups, characterised by different combinations of affected

Groups of patients according to distribution of muscle pain	Distribution of muscle pain: Back of the neck	Shoulder	Brachial	Hip- and gluteal	Thigh	Number of cases: Series A	Series B	Total
I	+	+	+	+	+	34	30	64
II	0	+	+	+	+	5	6	11
III	+	+	0	+	+	4	2	6
IV	+	+	+	0	+	0	1	1
V	+	+	+	0	0	4	1	5
VI	+	0	0	+	+	1	0	1
VII	+	+	0	0		1	0	1
VIII	+	+	0	+	0	0	1	1
IX	0	+	0	+	+	1	0	1
X	+	+	0	0	0	1	1	2
					Total	51	42	93

Tabl 17 Topographic distribution of muscle pain in 93 cases f PMA.

anatomic regions. This usually meant that the different regions had also been involved simultaneously during some part of the course of the disease, though with varying intensity.

Table 17 shows that in 64 (69 %) of the 93 cases all 5 regions, *viz.* neck, shoulders, upper arms, pelvic girdle and thighs were the site of myalgia and in 82 (88 %) at least 4 of these regions. Groups V—X comprised all together 11 cases (1 /) with myalgia in 3 or 2 of the above mentioned regions. The table also shows that in all the cases the brachio-cervical muscle groups were affected. This means that the 30 cases (Table 16) where myalgia was initially localised to the caudal muscle groups later also had pain in the brachio-cervical region, but not always the other way round because 7 cases (groups V and X in Table 17) never developed symptoms in the pelvic girdle or the lower limbs. Five of these patients belonged to series A and 2 to series B. The former had at the last examination been ill for 1—12 years and the latter for 1 1/ years. In 12 patients (groups II and IX) symptoms of myalgia of the neck never occurred and half of these belonged to each series. Of the 6 patients in series A, 1 was followed up for 8 months after the onset of the disease, the other 5 for 3—7 years. The 6 patients in series B without myalgia of the neck had been followed up for 2 to at least 7 years. Case 18 (series A) in group VI is noteworthy.

This 66-year-old man was observed from the very beginning of the disease in December 1961. He had severe myalgia of the neck, hips and thighs, initially also some pain in the lumbar spine and calves. At short intervals he was treated in 1962—1964 with prednisolone, during the major part of the period in small doses, and from the end of 1964 he has been symptom-free. He was often examined and never had pain in the shoulders or upper arms.

One patient in group V and both in group X were extreme cases: the myalgia was very local and very mild.

In case 78 (series B) in group V the patient was a 77 year-old man. He suddenly fell ill in February 1967 with severe headache, especially in the temporal region and with a maximum E. S. R. of 120 mm/1 hr. After he had been ill for 3 weeks he was admitted as an emergency to the department of internal medicine, clinical signs f temporal arteritis were suspected, but biopsy of the left temporal artery was negative. Treatment with prednisolone in dose f 40 mg/day controlled the symptoms within few days and the hor

mone was withdrawn after 2 weeks. The E. S. R. was then 37 mm/1 hr. The symptoms recurred in equal severity after a few weeks and the patient then had a stiff neck. The E. S. R. was 112 mm 1 hr. H. responded to 10 mg prednisolone a day just as promptly as on the first occasion. During the next few months he had *myalgia of the upper arms and shoulders.*

In case 80 (series B) in group X the patient was a 71-year-old woman. For 2 months she had had symptoms of right-sided periarthritis humeroscapularis and mild myalgia of the neck, fever and an E. S. R., which rose to 132 mm 1 hr. She had recei ed X-ray irradiation of the shoulder without any demonstrable effect. She responded to prednisolone in a dose of 5 mg a day. Treatment was withdraw after 4 weeks. A few months later she had very mild symptoms in the neck and the other shoulder.

Case 93 (series A) in group X was 71-year-old man who fell ill for 9 months with general but not rheumatic symptoms or headache. Aortic arch syndrome was diagnosed. Biopsy f the temporal artery showed arteritis. Not until about 1 year after the onset of the disease during pause in steroid treatment did he have mild myalgia in the neck, shoulders and possibly of the forearms.

G oups I, III and VIII in Table 17 comprise 71 cases with a "typical" distribution of myalgia. 38 of these cases belong to series A and 33 to series B. The proportion between typical and less typical cases regarding the distribution of myalgia was 38 13 in series A and 33-9 in series B ($p > 0.05$)

Impai ed mobility of cervical spine shoulders and hips

As pointed out previously (Chapter .), reduced mobility of the large joints in the early stage of the disease is probably due to pain. The longer the mobility of a joint is impaired the more the impairment appears to assume a mechanical charac ter *probably because of periarticular contractures.* Then the rheumatic pain generally abates. Both types of reduced mobility may occur simultaneously and to a varying degree in the course of the disease. In the following account an attempt is not made to deal with these two types of impaired mobility separately.

Examination of the patients evealed impairment of movement of one or more of the functions of the 5 joints examined in 81 of the 93 patients (T ble 18). If also the examined functions that had, according to the patients, previously been impaired be included, all patients except one would have had reduced mobility of at least 1 of the functions examined. In 8 patients all 5 joint functions were impaired, while if anamnestic impairment of function be included the number would be 37. In the same way bilateral reduction of mobility was noted for the shoulders and the hips in 18 patients at the examination, *while a further 9 patients had had re*duced mobility of these 4 joints, as judged from their history before admission to hospital. Table 18 thus shows the previously mentioned observation that some patients were incapacitated more during the months before admission to hospital than later.

In Table 19 the material is distributed according to the number of cases with bilateral, unilateral or no reduction in range of movement of the shoulder and hip joints during the observation period.

Table 20 surveys the material according to the number of cases with an objectively demonstrated impairment of movement and the number of cases with such impairment including those cases with

Joints with impaired mobility		*No. of case with impaired mobility in stated joint*	
N of joints	Involved joints	At examinations	From history and examinations
5	Shoulders, hips, cervical spine	8	37
4	Shoulders, hips	18	27
4	Shoulders, one hip, cervical spine	1	1
3	Shoulders, cervical spine	19	9
3	Shoulders, one hip	1	0
3	One shoulder hips	1	1
3	One shoulder one hip, cervical spine	1	0
3	Cervical spine, hips	1	3
	Shoulders	17	5
2	One shoulder cervical spine	4	2
2	Hips	3	0
1	One shoulder	3	1
1	Cervical spine	4	6
0	— — —	12	1
	Total	93	93

Table 18. Distribution of 93 cases of PMA ith regard to impaired mobility of shoulder and hip joints and in cervical spine (as judged from the angle through which the head could be turned). The table is based on anamnestic data and examination findings.

Involved joints	Number of patients		
	Impaired mobility		Without impaired mobility
	Bilaterally	Unilaterally	
Shoulders	64 (69)	9 (10)	20 (22)
Hips	31 (33)	3 (3)	59 (63)

Table 19 Impaired mobility of shoulders and hips among 93 cases of PMA at examinations. Figures in brackets denote percentage of whole material.

Involved joints	No of cases with impaired mobility in stated joints	
	At examinations	From history and examinations
Shoulders	73 (79)	83 (89)
Hips	34 (37)	*69 (74)*
Cervical spine	38 (41)	58 (6)

Table 20. Patients with bilateral or unilateral impairment of mobility of the joints in 93 cases of PMA. Figures in brackets denote percentage of whole material.

previous impairment according to the patients records. Impairment of movement was observed roughly twice as often in the shoulders as in the cervical spine or hips, but this difference was much smaller when also anamnestically reported limitation of movement was included.

In Table 21 the material is divided into series A and B and each series is divided into 4 classes according to the number of joints, whose range of

	Number of patients with impaired mobility of				
	4—5 joints	—3 joints	1 joint	0 joint	
Patients in series A	15 (36)	3 (11)	3 (3)	10 (1)	51
Patients in series B	12 (29)	4 (9)	4 (4)	2 (0)	42
	7 6)	47 (20)	7 (7)	12 (1)	93

Table 1 Distribution of 93 cases of PMA with regard to the number of joint ith impaired mobility at examinations referred to are shoulders, hips and cervical spine judged from the angle through which the head could be turned) Figures brackets refer to data gained from xamination and anamnestic information

movement was found to be limited at the examination. In addition, the numbers are given in each class if also anamnestic information be included. When the two last classes were pooled in Table 21 3 classes were obtained representing the number of cases with limitation of movement of 4—5 2—3 and 0—1 joints. In the homogeneity test with chi-2-method of the figures without brackets, and of the figures within brackets, the chi-2-value obtained was 2.2 and 0 1 respectively (chi 2 = 5.99 for p = 0 05 and DF) Thus no significant difference was found between series A and B regarding the proportions of cases with impairment of movement in 4—5 2—3 and 0—1 joints, respectively whether only impairment seen at the examination be considered or if also previous impairment reported by the patient also be taken into account.

Duration of impairment of movement

As mentioned in Chapter 3 entries were continually made in the diagram of the course in each patient. The rheumatic symptoms were classified according to 4 degrees of severity With the aid of the diagrams it was possible to determine the duration of limitation of movement of one or more of the joints examined. This period depends mainly on the symptoms in the shoulder joints, since it was in these joints that the impairment lasted longest

During the observation period 78 (84 %) of the 93 patients received steroid therapy (48 in series A and 30 in series B). 69 / of these 78 patients had had impairment of mobility for less than 6 months before the beginning of steroid therapy 27 % for 6—12 months and 4 % longer than 12 months. No significant difference was found in mean duration of impaired mobility before steroid therapy between series *A* and *B* by using *t-test.*

The shorter the time the patient had had impairment of mobility the quicker it was controlled by steroid therapy In an inveterate case, on the other hand, the reduction of mobility responded only little if at all, to steroid therapy per os. At the last examination impairment of movement was noted in 4 patients in each of the 2 series, and all 8 showed the picture of a frozen shoulder of varying severity All 8 except 1 in series A had received steroid therapy At the last examination the limitation of movement had persisted continuously for 5—12 months in the A-cases and from 18—29 months in the B-cases.

Rheumatic symptoms and signs	Number of cases					
	Series A			Series B		
	M	F	M+F	M	F	M+F
Back pain	8	8	16	3	6	9
Symptoms and signs from the hands	12	18	30	7	15	22
Swelling of the hands	5	4	9	5	11	16
Reduced extension of the elbow joints	3	2	5	1	2	3
Symptoms and signs from the knees	10	13	23	6	11	17
Effusion in the knees	3	1	4	2	1	3
Calf pain	6	5	11	5	10	15
Symptoms and signs from the feet	1	6	7	2	7	9

Table 22. *Subjective and objective rheumatic symptoms* in 93 cases of PMA with less characteristic sites of symptoms

Other rheumatic symptoms

Rheumatic symptoms, though usually much less severe, occurred also in regions other than those discussed above (Table 22). The frequency figures given in this table for the rheumatic symptoms in distal portions of the limbs and back are minimum values because the mildest and most transient symptoms were not recorded.

Back pain was noted in 25 of the 93 cases (27 %). In most of them it was pain on movement and low back pain.

Clumsiness and stiffness of the hands and fingers, especially on awakening in the morning, were common and occurred also in the absence of objective changes. Paresthesia of the fingers was noted in several cases in a later stage of the disease and had the character of an arterial insufficiency symptom, which occasionally increased to pain after working with the arms. Sometimes paresthesia also occurred early in the disease but it was difficult to say whether this was a manifestation of arterial insufficiency because owing to pain in the shoulders and upper arms it was not possible for the patients to do any work with their arms. Symptoms of varying character and intensity in the hands occurred in 52 (56 %) of the cases. The distribution of these cases in the two series did not differ significantly from one another.

Swelling of the hands was noted in 25 (27 %) of the cases and more often in series B than in series A. This difference between the series was statistically significant (chi-2 = 4.90, DF = 1, p < 0.05). The typical swelling consisted of diffuse oedema over the backs of the hands and of the fingers. The swelling varied from limitation of movement by tense oedema to barely discernible oedema. In some of these cases the skin was wrinkled after oedema. The oedema of the hand usually disappeared without leaving behind any changes but in some cases there was a fibrous streakiness subcutaneously, best seen in the ulnar part of the palms. These changes resembled mild forms of Dupuytren's contractures.

In 8 (9 %) an extension defect of the elbow was noted on one or both sides. In none of the cases was the extension defect permanent.

In 40 (43 %) of the cases symptoms were recorded in the region of the knee, but if also vague symptoms had been included, the number would surely have been higher. The knee symptoms appeared to be periarticular and particularly characteristic was the tenderness over the insertion of the medial flexor group in the tibia. In this region the soft tissues were often clearly swollen. No attempt was made to calculate the frequency of such swelling because the palpatory findings are often uncertain, particularly in corpulent persons. In 7 (8 %) of the cases there was effusion in one or both knee joints. In 4 of these cases the effusion was verified by puncture. Two of the patients with effusion also had considerable arthrosis of the joint.

Mild symptoms of the lower arms and calves were not uncommon. In some cases the volar aspect of the wrists and forearms were mildly to moderately oedematous. Occasionally — particularly in case 5 — there was a swelling along the course of the radial artery and the ulnar artery suggesting involvement of these very vessels. A corresponding suspicion was also suggested by the calf in case 33 (published as case No 1 in a previous publication by Hamrin et al. 1968). That patient was a 65 year-old woman who was referred to the department because of assumed deep venous

thrombosis of the right leg. She did not respond adequately to conventional treatment. For several weeks a well defined tender lump (about 12×5 cm) was palpated along the deep essels of the calf

Symptoms in the feet were recorded in 16 (17) of the cases. In some of these the feet were also swollen.

The rheumatic symptoms peripherally to the upper arms and thighs usually disappeared within some weeks. Only rarely did they persist for months. They did not leave behind any permanent limitation of movement of the joints except in case 28 which is described in the next chapter

Those cases of shoulder-hand syndrome (Table 23)

Shoulder-hand syndrome	Number of cases					
	Series A			Series B		
	M	F	M+F	M	F	M+F
Type I	1	2	3	.	3	5
Type II	1	1	2	1	2	3
Total		3	5	3	5	8

Table 23 Shoulder-hand syndrome among 93 cases of PMA. Type I denotes cases with both swelling and impaired movement of the hand joints; type II, cases with only swelling of the hands.

in the material were divided into two types, namely type I, characterised by limitation of movement from one or both shoulders and swelling of homolateral hand or both hands in association with inability to clench the hand completely because of oedema of the hand and fingers, and secondly type II with changes as in type I but without such inability There were all together 8 cases of type I and 5 of type II. Shoulder-hand syndrome was less common in series A than in series B but the difference was not significant.

Though a sharp watch was kept for cases with subcutaneous nodules no such nodules were ever found.

Roentgen examination of hand skeleton

In 73 (78) of the patients the hands were examined roentgenographically 38 (52) of these patients belonged to series A and 35 (48) to series B The roentgen examination was performed in 38 (5) of the 3 patients more than 2 years after onset. I ate in the course and in some cases the patient had in the meantime clinically recovered. For comparison hands of 64 controls were also examined roentgenographically Apart from one case of arthropathia psoriatica (Chapter 8) neither the patients nor the controls showed any clearly arthritic changes in the hands at these examinations.

Comments

Examination for rheumatic symptoms and signs is timeconsuming and the methods are not very exact. For old patients and patients in a poor general condition these examinations are also tiring and troublesome These drawbacks are particularly prominent in PMA, in which the rheumatic symptoms are largely subjective.

By standardising the examination methods and limiting examination of joint function to the shoulders, hips and regarding the cervical spine, only to turning of the head it was, however possible to combine these frequently repeated examinations with likewise time-consuming physical examination of peripheral arteries and bilateral measurements of the blood pressure (Chapters 9 and 10). In order to save time only passive movement of the joints was studied systematically which reduced the cooperation of the patients at the examination. Testing of the range of movement was done as systematically as possible, and by the author himself. A comparison between different groups of the material therefore appears permittable which it would hardly have been if the examinations had been carried out by different examiners because the differences in examination technique between different examiners in this type of rheumatic symptoms would result in far too wide a variation of the results, a variation which could hardly be corrected for

A search of the literature failed to reveal any tables of the normal range of movement of the tested joints in various age groups. The values used (Chapter 3) were based on examinations of a small number of elderly persons without previous or existing symptoms of rheumatic disease. They were not included as a requirement for the later selected control material. It was, however found that all the controls filled the requirements of normal range of movement of the cervical spine, shoulders and — with reservation for the difficulty in assessment — of the hips.

GENERAL SYMPTOMS

A poor general condition is common in the disease and the systemic symptoms are often striking and vary with the intensity and duration of the disease. The patient's general condition is poorest during the first —3 months of the disease and may dominate the picture. In patients with a subacute onset of the disease the patients are sometimes really ill before the appearence of the rheumatic pain but such a short effect on the general condition before the rheumatic symptoms is difficult for the patient to describe or define precisely. As mentioned in 4 cases there was a long prodromal stage during which local symptoms were missing and for months the disease had the character of a wasting systemic disease of obscure nature.

Fatigue — Fatigue is often severe and characterised by apathy which makes it difficult to get a proper history. A depressive and resigned attitude of the patient is also common, and at least sometimes such an attitude is justified by the patient's conviction or suspicion of having a malignant disease in an advanced stage. Fatigue was denied by only one of the 93 patients. That patient was a 56-year-old man in series B with a fairly mild course but not deviating from other cases. The E. S. R. was at most 79 mm.

Anorexia — Information about the patient' appetite is missing in 2 cases. Of 91 patients, 10 reported that their appetite had not been affected. Four of these belonged to series A and 6 to series B.

Loss of w ight — In 34 cases no reliable information regarding possible weight loss was available. In 59 (63) of the 93 cases it was, however possible to obtain information about the loss of weight (Table 24). In some cases the patients could

Weight loss (kg)	Number of cases					
	Series A			Series B		
	M	F	M + F	M	F	M + F
2—6	9	5	14	3	6	9
6—6 9	1	6	7	2	3	5
10—13 9	3	5	8	2	7	9
14	3	3	6	0	1	1
Total	16	19	35	7	17	24

Table 24 Loss of weight during the disease in 59 (63) of 93 cases PMA.

thus give reliable information about his weight before the disease and in these the loss of weight was calculated as the difference between the weight reported by the patient and the lowest weight of the patient in the hospital records before steroid therapy. In those cases where the patients could not give any information about their habitual weight, loss in weight was calculated simply from the difference between the highest and lowest weight noted in the patient's hospital records.

It is clear from Table 24 that 36 (61) of the 59 patients lost at least 6 kg and 24 (41) at least 10 kg. One patient (case 5) lost as much as 17 kg. That loss in weight was often considerable is also apparent from the fact that several patients increased considerably in weight after they had recovered. Thus, patients Nos 7 and 17 put on 11 and 20 kg, respectively. In these two cases no information is available as to the amount of weight they had lost. In case 56 the patient had lost 3 kg before the beginning of steroid therapy. From the lowest value the patient increased by 15 kg in weight and kept this weight after the small steroid dose was withdrawn after 2 years.

The mean difference between series A and B was tested by t test and no significant difference was found.

Fever — Fever nearly always occurs some time during the disease, but may be readily missed if the patient is not hospitalised in the early stage of the disease. In most cases the increase in body temperature is only small, but prolonged. Many of the patients do not experience their disease as a febrile condition and therefore do not check their temperature egularly.

Only in a few cases was high grade fever recorded, and then usually in the beginning of the disease.

The material was divided into 4 classes according to the highest rectal temperature recorded (Table 25). In 10 of the cases the temperature was that measured at home but was reliable, and in the remaining 83 cases it was the highest noted during the patient stay in hospital. In 15 cases (16) body temperature was as high as 39 or more and the highest value measured in any of the patients was 40.0 . In series A 38 patients hade fever (≥38°) and 13 were subfebrile or afebrile. The corresponding figures for series B were 26 and 16. This difference between the series was not significant.

thrombosis of the right leg. She did not respond adequately to conventional treatment. For several weeks a well defined tender lump (about 12 ×5 cm) was palpated along the deep vessels of the calf

Symptoms in the feet were recorded in 16 (17) of the cases. In some of these the feet were also swollen.

The rheumatic symptoms peripherally to the upper arms and thighs usually disappeared within some weeks. Only rarely did they persist for months. They did not lea e behind any permanent limitation of movement of the joints except in case _8 which is described in the next chapter

Those cases of shoulder hand syndrome (Table 23)

Shoulder-hand syndrome	Number of cases					
	Series A			Series B		
	M	F	M+F	M	F	M+F
Type I	1	2	3	_	3	5
Type II	1	1	_	1	2	3
Total	2	3	5	3	5	8

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common. If also mild transient swelling be included, about every fourth patient had swelling of their hands and a few also swelling of the feet. If morning stiffness and paresthesia be included more than half of the patients had symptoms of the hands.

Extension defect of the elbow of slight or moderate severity was observed in a small number of cases and appeared to be due to contractures of the biceps musculature.

Pain on movement of the knee joints and tenderness over the tendons in the kneefold were common symptoms. Sometimes periarticular swelling was observed medially over the knee. In 7 patients there was effusion in the knee joint which was confirmed by puncture in 4

Most patients received steroid therapy Before such therapy was started about two thirds had *limited* range of motion of one or more of the joints examined for less than 6 months and the remainder for more than 6 months.

During some period of the disease 14 / of the patients exhibited a picture of uni or bilateral shoulder-hand syndrome

In addition to the raised E. S. R. the following constitutional symptoms and signs were observed.

All or almost all experienced fatigue and anorexia.

Loss of bodyweight was common and sometimes considerable. Of the patients from whom data were available 41 had lost at least 10 kg

Mild or moderate and prolonged fever was the rule I two thirds of the cases temperatures of 38 or more were noted and 16 / had temperatures above 39

ILLUSTRATIVE CASES

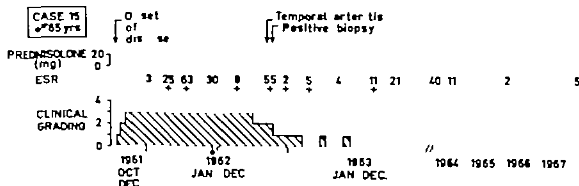
A characteristic, and moderately severe case of PMA is described in Chapter 3 The following cases exemplify the various forms and courses of the disease.

Case 15 O F (Fig. 9). — A 65-year-old factory worker who had previously always felt well, fell ill on the 15th of October 1961 with increasing pain in the shoulders, especially on the right side. The pain increased, and 1 month later he sought medical advice. H was first given short-wave therapy and periarticular injections of cortisone into the right shoulder but without demonstrabl effect. In January 1962 *right sided hum roscapular periarthritis* was diagnosed. Roentgenray treatment f the shoulder was followed by temporary relief. At the end of December 1961 pain supervened in the groins, in the muscles of the pelvic girdle and in the flexors f the thigh down to the kneefold. The myalgia of the hips and legs became worse. In February 1962 the patient's doctor discovered that the knee and ankle jerks could not be elicited on either side and *organic nervous disease* was suspected.

I the latte half of March 1962 the patient was admitted to the department of internal medicine for investigation of suspected neurological disease. He spent 3 weeks in hospital. During this time his body temperature was continuously slightly increased. Movement f the shoulders and hips was markedly limited. H walked with somewhat forward bend and careful steps without turning his head and with poor accompanying movements of the arms. Apart from a positive

Fig. 9 Graphic demonstration of course in case 15 Clinical grading as judged from intensity of pain and reduction of mobility essentially according to Gordon (1960). Grade 4 severe pain with reduced mobility of neck, shoulders and hips. Patient severely disabled. Grade 3 moderate pain with reduced mobility of at least one of these joints. Grade 2 mild, but constant, pain requiring continual use f analgesics. Grade 1 mild, inconstant pain requiring analgesics at most occasionally

♦ denotes time of diagnosis.



Lasègue on the right side and absence of patella and achilles reflexes, neurological examination revealed nothing abnormal. Meinicke and W R. in the blood were negative. (The patient had been admitted to hospital for some weeks in 1944 because of ischias dx. His records from that time contained notes about a normal Lasègue's test and normal tendon reflexes.)

Laboratory studies — The highest E. S. R. recorded was 64 mm/1 hr which was noted in the fifth month of the disease. At the same time the serum protein was 6.7 g/100 ml and the concentration of the paperelectrophoretic fractions in grams per 100 ml were as follows albumin 3.32, α_1-globulin 0 43 -globulin 0.88 β_1-globulin 0.37 β_2-globulin 0.49 γ-globulin 1.21 Haemoglobin was 13.8 g/100 ml. White blood cell count 13 100 and eosinophils 205 per μl. Myelography revealed no intervertebral hernia and the rootpockets appeared normal. The protein content of the C. S. F was possibly increased (66 mg per 100 ml).

During the first half of 1962 the shoulders and the hips were examined roentgenographically At the first examination in January *several calcifications* were observed in the soft tissues outside the greater tubercl *in the right shoulder* Five months later these calcifications were no longer demonstrable, but *small calcification* had appeared periarticularly *in the left shoulder* In March *an oblong calcified mass* was observed outside the greater trochanter *in the left hip joint*

Course — At examination on June 20 1962 PMA was diagnosed. The shoulders and hips were still painful and stiff and the patient found it difficult to stand up from the sitting position. During the summer and the autumn the patient's condition improved except in the left shoulder which had become stiff. The E. S. R. had become normal.

Some months in the autumn of 1962 the shoulder symptoms became predominant, and then the condition showed the picture of *peritendinitis calcarea humeroscapularis sin.*

The patient had practically entirely recovered from his rheumatic pain when in the beginning of November 1962 he suddenly had neckpain and headache. The pain was worse inside the ears" and the pharynx which, at examination on November 14, 1962, appeared normal. The temporal arteries and their branches were markedly swollen, reddened and tender On the right side the arterial pulsations were weak on the left side not palpable. Biopsy of the left temporal artery showed a microscopic picture of giant-cell arteritis. Treatment with prednisolone was started with a relatively small dose and was stopped after 2 years. During the following 4 years after withdrawal of prednisolone the patient has been symptom-free.

Comments — This was the only case of classical temporal arteritis observed by the author in the series. The signs of temporal arteritis appeared, when the polymyalgic symptoms had nearly disappeared

The case illustrates the fact that PMA may dur ing certain phases of the disease be impossible to distinguish clinically or roentgenologically from periarthritis. The case also shows that PMA may be accompanied by only a moderate increase of the E. S. R. The case is also interesting from a neurological point of view

Case 83 K Y (Fig. 10). — The patient was a 75-year-old, unmarried woman who had previously felt well. The onset was subacute. In September 1966 she developed pain and stiffness of the neck, pain in the muscles of the posterior side f the right thigh and in the region of the right buttock, in the region f the left groin and in the anterior part of the left thigh. After few weeks she also had pain in the shoulders and upper arms. Owing to pain on movement of the joints she

Fig. 10. Clinical course in case 83 For explanation of the diagram, see Fig. 9

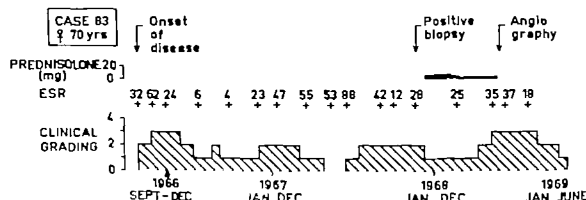




Fig. 11 The left subclavian and axillary arteries have a narrow lumen which is obvious when compared with the normal brachial artery. The most distal part of the xillary artery is especially narrow with small irregularities of the wall, which otherwise ppears rather smooth. Marked stenosis f the first part of the erte bral artery (arrow). (Case 81). (Cf Fig. 28 Chapter 10).

soon found it difficult to dress, but then and even later she could manage alone. The myalgia of the hips and thighs abated after about a month. She had sought advice from various physicians and had been treated for *periarthritis humeroscapularis dxt* — the right shoulder had been worse.

At examination of the patient on November 4 1966 she had fairly marked limitation of movement of shoulders and the cervical spine. She reported spon taneously that during the last few weeks she had had a sensation of "prickling inside the right ear" and that during the last few days she had sensation of "tingling in the arteries in the right wrist. Palpation f the temporal arteries revealed nothing remarkable. PMA was diagnosed. The patient refused steroid therapy

Course — The next half year the heumatic symptoms improved and the E S R. fell to 4 mm. In the summer of 1967 the myalgia of the neck, shoulders, and above all the hips and thighs again became worse and the E S R. began to rise. She complained of pain most over the symphysis, in the groins and the adduc tors f the thighs. In the autumn of 1967 the myalgia bated. But at the same time the E. S. R. rose and the patient lost 5 kg that autumn.

The patient was admitted to hospital and observed for 3 weeks, between December 1967 and January 1968. The symptoms of myalgia were extremely mild. She looked pale and tired. She was subfebrile.

Laboratory studies. — On admission the E. S. R. was 74 mm/1 h and the plasma fibrinogen 0.71 g/100 ml. Serum protein was 7.3 g/100 ml and paper electrophoresis showed the following values in g per 100 ml serum for the different fractions albumin 4.11 α_1 globulin 0.34, α_2-globulin 0.85 $\beta_1$globulin 0 44 β_2 globulin 0.37 γ-globulin 1.21 Haemoglobin 11.2 g/100 ml. Red blood cells 3.8 million, white blood cells 6,000 *and eosinophilic leucocytes 344/µl.*

Ther was reason to suspect malignant disease, but no such disease could be demonstrated.

During the winter and spring of 1968 the patient had moderate migrating myalgia. In March 1968 mur murs wer heard over the xillary arteries bilaterally for the first time (Chapter 9). The temporal arteries pulsated still in a normal way In May 1968 biopsy of the right temporal artery showed uncharacteristic ar teritis. Prednisolone was started in a small dose which as reduced still further after few months by when glycosuria and mild diabetes had been diagnosed. The reduction and withdrawal of prednisolone was accompanied by increasing intensity of the symptoms, espe cially in the left shoulder and the patient then showed

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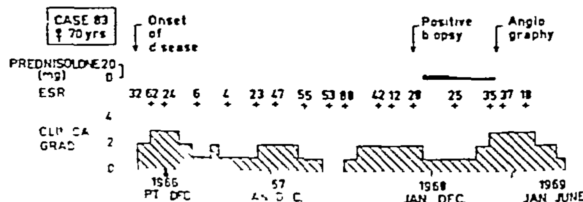
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Fig. 10. Clinical course in case 83. For explanation of the diagram, see Fig. 9.



of the wrists. The wrists were tender to palpation. The hands had been swollen during the first spell, but barely during the recurrence in 1966. Roentgen examination showed no arthritic changes of the hands and only moderate arthrosis of the knees, hips and shoulders. Steroid treatment was given locally in the knee and around the shoulders but the best effect was noted on systemic treatment per os with prednisolone which was started in March 1968.

After barely 2 years disease auscultation over the left subclavian artery revealed weak murmur and over the left axillary artery a stronger murmur. During the following years multiple murmurs appeared on both sides over the subclavian, axillary, brachial and carotid arteries. A weak murmur appeared also over the popliteal artery in 1964. During the recurrence in 1966—1968 the murmur over the left popliteal artery became very loud.

Comments. — This patient had two spells of myalgia, the second 5 years after the first. The second attack developed slowly. During its development the knee symptoms were sometimes predominant and then rheumatoid arthritis appeared reasonable. The constellation during this spell with effusion in the knee joint as a sign of synovitis and a gradually developing very strong stenosis murmur over the popliteal artery on the same side was suggestive. Especially the chronology of these phenomena suggested a causal relationship. The entire course of the disease left the impression of arteritis of low activity between the attacks of polymyalgia.

DISCUSSION

The discrepancy between the severe pain recorded and the relatively insignificant objective findings at examination is often striking. A thorough inquiry into the patient's history often leaves the impression of a severe, protracted disease before the patient is first seen by the physician and this history is often informative and facilitates recognition of the disease. *A proper conception of this disease requires close observation of a number of patients for a long time.*

The criteria set up in the present investigation characterise the main features of the disease. It should, however, be stressed that within the limits defined by these criteria, the clinical picture may be very polymorphous. This holds on comparison between different cases and for a comparison of the disease on different occasions in one and the same patient. Chapter 3 described a characteristic case of PMA (case No 4). This case agreed well with descriptions of cases of polymyalgia rheumatica with an uncomplicated course of moderate severity. But not all cases are so typical in all respects. It is thus natural that if a patient has severe pain in the neck alone or one shoulder he will mention this and forget about milder symptoms in other regions.

Moreover, during certain periods of their disease some patients have only symptoms worth mentioning in one hip or the neck or more often one shoulder. This is exemplified by cases 15 and 83. Such cases are then inclined to be diagnosed as periarthritis, "frozen shoulder" or the like and if the symptoms in the neck are predominant, torticollis. If a patient has simultaneous symptoms in the neck and one shoulder the condition is liable to be diagnosed as cervical rhizopathy, especially as most patients in this age group have a certain degree of roentgenologically demonstrable spondylosis. Paresthesia, usually probably due mainly to arterial insufficiency is also a common symptom in PMA.

As for the extent and intensity of the myalgia, it varies widely from protracted widespread myalgia, as in case 83 and even severe symptoms as in case 4 (Chapter 3) to such mild symptoms as barely to fill the diagnostic criteria, as in cases 78, 80 and 93 referred to above.

The term polymyalgia in the strict sense of the word means localisation of pain to the muscles. The advantage of the name is that it is relatively short, but it does not satisfactorily describe the localisation of the pain because such pain may be severe in the tendons, bursae and in periarticular structures. If a patient with myalgia is asked whether he has the pain in the joints or in the muscles, some will probably answer in the muscles, while others find it difficult to decide but after some doubt say the joints (Hamrin et al. 1964). The answer to these questions, however, vary during the course of the disease. On palpation there is usually only a slight to moderate tenderness of the muscles. Around the shoulder and hip joints it is difficult to decide whether the tenderness is localised to the strong muscles in these areas or to tendons and other periarticular connective tissue. It would, however, appear that the tenderness is most severe and often limited to a small area at the level of the subdeltoid bursa, around the greater tubercle along the long biceps tendon or

pectoral tendon in the shoulder or the area of the greater trochanter in the hip and flexor tendons in the knee fold

With the examination frequency used in the present investigation it was found that most of the patients with PMA had more or less pronounced rheumatic symptoms in the regions peripheral to the shoulders and hip joints during their disease. Sometimes these symptoms were considerable as in case 7 in which the clinical picture during some part of the disease resembled that of rheumatoid arthritis. Our conception of rheumatoid arthritis is, however imperfect since the symptoms and the course in this syndrome vary so widely and since the aetiology and pathogenesis are not properly understood.

In order to distinguish rheumatoid arthritis as clearly as possible, the American Rheumatoid Association (Ropes et al. 1958 McEwen in Arthritis and Allied Conditions by Hollander 1969) suggested certain criteria for the diagnosis. They also recommended grouping of cases with rheumatoid arthritis in 4 classes namely classical, definite probable and possible rheumatoid arthritis, all according to the number of criteria filled by a given case. According to the American suggestion the diagnosis requires also exclusion of certain cases including unilateral shoulder-hand syndrome and polyarteritis nodosa. But their suggestion includes nothing about the syndrome of polymyalgia or the clinical features of temporal arteritis forming a subject of discussion to-day in Europe

In the collection of the present material of PMA the cases were not classified according to the suggestion of the American Rheumatism Association. In the description of materials of rheumatoid arthritis these diagnostic criteria are, however often used. *Without classifying the present cases in de*tail according to the American Rheumatism Association diagnostic criteria for rheumatoid arthritis it might therefore be of interest to state that many of the patients in the present material of PMA certainly filled the criteria for possible and probable" rheumatoid arthritis. It is also probable that several cases could be accepted as definite rheumatoid arthritis on clinical symptoms and signs alone. But none of the cases filled the requirements of classical" rheumatoid arthritis. Despite an observation period of up to 7 years in the present series — often also for a further years — none of the cases developed deformities of the hands with ulnar deviation of the fingers in the metacarpophalangeal joints or other deformities of the wrist and hand characteristic of advanced cases of rheumatoid arthritis. As a matter of fact no permanent or characteristic arthritic changes were seen in the hands with the exception of one case of arthropathia psoriatica. This case is accounted for in the next chapter

Despite a continual watch for such changes no subcutaneous nodules were seen

The analysis of the rheumatic symptoms in the present material as well as of the patient histories showed that the symptoms of PMA both on comparison between different cases and between different stages of a given case, may vary from migrating myalgia and pictures impossible to distinguish from periarthritis of the shoulder or hip to diseases resembling rheumatoid arthritis. From a nosological point of view it is therefore easy to understand why opinions about the relation of polymyalgia to other rheumatic diseases has pendulated from the view that it is a severe form of humeroscapular periarthritis (Meulengracht 1945) to the view that the disease is an atypical form of rheumatoid arthritis, a form which Bagratuni called anarthritic rheumatoid disease (1956 and 1963). The present material of PMA was collected in an area where the range of specialities represented by the hospitals was fairly low there were thus no special departments of orthopaedic surgery or rheumatology. With the wide range of diseases referred to our department, the diagnostic requirements of PMA of bilateral symptoms in the shoulders or hips appeared arbitrary because sometimes patients were seen with unilateral periarthritis and, apart from the fact that the symptoms were one sided, filled the requirements. Distinction from *rheumatoid arthritis appeared less subjective and* usually did not require long observation

As for the occurrence and frequency of various symptoms and features of the clinical picture of PMA, the reader is referred to a recent survey by Hunder et al 1969. In most investigations the patients have been selected on the basis of a more and more distinct and detailed description of the disease. There appears to be good agreement among a large number of authors concerning the cardinal symptoms and course of the disease but it is obvious that selection of the patients has been biased by various factors. Especially the average severity of the disease reflected in different values

Manifestations	Gordon 1960 (n=21)	de Sèze et al. 1965 (n=45)	Hamrin 1972 (n=93)
Acute onset of disease	76	40	40
Primarily affected muscles			
brachio-cervical	52	57	63
caudal	48	21	34
Topographic distribution of rheumatic symptoms and signs			
shoulders	100	100	99
neck	—	67	87
hips	—	91	90
hands, wrists	43	42	56
knees	43	38	43
knee joint effusion	5	0	8
feet	0	13	17
Fever	57	49	92
Loss of weight	91	76	100

Table 27 Symptoms and signs in two published series and in the present material. I Gordon series the values are percentage of the whole material, in the other two series, all or almost all cases, except for fever and weight loss, for which data were unavailable in a small number of cases

of the E. S R varies f om series to series. Only a few authors give strict criteria for the diagnosis, but these differ from series to series. It might ne vertheless be of interest to compare the present series of PMA with two published series regarding the frequency of rheumatic and other symptoms (Table 27) Gordon (1960) gave a detailed analysis of the clinical picture and de Sèze et al. (1965) presented a material that had been thoroughly studied (Chapter) The topographical reco ding of the rheumatic symptoms in these investigations are, it is true, similar to that in the present material but d ffer somewhat in other aspects, so that minor approximations must be made in Table 27 Since evaluation of the symptoms is based on the patient's description and since the signs are often subtle the agreement between the two publications referred to above and the present material concerning the frequency of symptoms is good

In the earliest descriptions of polymyalgia (Bruce 1888 Meulengracht 1945 Holst & Johansen 1945 Kersley 1951 Porsman 1951) symptoms n the knees and minor joints received less attention Bagratuni (1953 1956 and 1963), however regarded such symptoms as signs of the disease being an abortive f rm of rheumatoid arthritis In later publications rheumatic symptoms of peripheral parts of the limbs are regularly described. Especially Bruk (1967) discussed such symptoms He found capsular swelling with or without effusion into the knee in 50 / of the cases, in sternoclavicular joints in 40 /, in acromioclavicular joints in 19 / and in the wrists in 12 /. At biopsy of the sternoclavicular joint in 5 cases, all 5 showed non-specific synovitis. Bruk, however reported that synovitis was usually transient and occasionally lasted only a few days His observations thus agree with those reported by other researchers, i that the symptoms in minor and peripheral joints are mild and transient compared with those in the shoulder girdle, neck and hips Neither do Bruk's observations argue gainst the conception that the disease is mainly periarticular it being well known that also in humeroscapular periarthritis there is non-specific acute or chronic inflammation both periarticularly and in the synovia (Codman 1934 Simmonds 1949 Lippmann 1951 DePalma 1952).

Except for swelling of the hands, no significant differences were found between series A and B regarding the various symptoms and signs studied But only series A provided evidence for the hypothesis of the pathogenetic role played by arteritis in PMA.

FURTHER CLINICAL OBSERVAT

Some of the patients belonging to the early part of the series were found to be troubled by disturbances of the gustatory or olfactory senses In addition, one patient, likewise belonging to the early part of the series, had fairly troublesome pruritus. In that patient liver function was also impaired, but there was no jaundice (case 18). At history taking all of the subsequent patients were therefore questioned concerning itching and disturbances of the senses of taste and smell. This chapter concerns an analysis of the answers obtained and of some other clinical observations made in the material

NEUROLOGIC SYMPTOMS AND SIGNS

Cases complicated by eye symptoms have been accounted for in a previous section

Disturbances of the gustatory or olfactory senses Of the 93 patients, 85 (91 /) were questioned concerning alterations in the senses of taste and smell, and 39 (46 /) answered in the affirmative (*Table 28*). Dysgeusia and/or dysosmia was noted in 21 (44 /) of the patients in series A and in 18 (49 /) of those in series B These figures are based entirely on the patients reports, no attempt having been made to test the patients senses of taste and smell.

Some patients appear to have an isolated and well defined impairment of perception, while in others the disorder was more complex. Ageusia was diagnosed if the patient reported that he could no longer distinguish the different tastes of the various ingredients of his meals. Ageusia was sometimes followed by parageusia, which, however occasionally developed without preceding ageusia. In

Disturbances of the senses of taste and smell	Series A M	F	M+F	Series B M	F	M+F
Present	10	11	21		1	18
Not present	12	15	27		3	19
Total	22	26	48		4	7

T ble 28 Disturbances of the gus... or lfac tory senses in 85 (91 ... with ... A

one case of parage ... mple, all food, even sugar tasted bitter ... e as in case 18 or as salt, as in cases 8 ... rageusia was sometimes selective, i e ... in substances tasted different many pat ... pped drinking coffee which they thought ... ier one patient (No 2) felt that sugar was ... tasteful, and another (No 49) that sugar ta ... r In cases of parosmia (Nos 7 and 5) ... thing smelt disgusting Anosmia or parosmia ... d inveterate smokers to stop smoking (Nos 17 and 93)

The disturbances f the senses of taste and smell usually occurred within the f rst month of the disease and were never permanent Characteristic of the disorders was that they responded promptly to steroid therapy

Other neurologic disorders In one patient, a man, aged 72 and belonging to series A (case 36) a peripheral facial paresis occu ... fter he had had PMA for three months ... s had notably regressed before initiat ... d therapy In case 15 the only neur ... observed was loss of the knee ... is case is reported in Chap ... reaction in the blood was n ... fore onset of PMA these ... to hospital records, been

Dizzine ... is commo in the age ... resent p tients bel ... ys not in the re ... ng to number ... hic however ... he clavian ... r then us after its illustrat Chapte phy rev Dizzine fairly sease ing th times Thus 43 r

Case No.	Se	Protein reactions			Number of cells per 3.2 μl.		
		Nonne	Pandy	Total protein mg/100 ml	Poly	Mono	R. B. C.
Series A							
4 (I)	M	traces	+	85	6	8	3
4 (II)		traces	+	56	0	4	12
15	M	traces	traces	66	0	2	0
93	M	0	0	72	2	2	6
Series B							
13	F	0	0	55	0	4	0
65 (I)	M	0	0	58	8	40	53
65 (II)		0	0	65	2	1	3

Table 29 Positive or doubtfully positive findings in lumbar cerebrospinal fluid from 5 patients with PMA. The Roman figures denote the order of the examinations.

patients in the Malmö material of histologically verified temporal arteritis reported dizziness in association with the disease (Chapter 12).

Examination of cerebrospinal fluid

Cerebrospinal fluid was obtained in 18 cases, most of which belonged to the 23 published previously (Hamrin et al. 1964). In two (Nos 4 and 65) the C. S. F. was examined on two occasions. In most of the cases the examination of the C. S. F. was performed because changes in the C. S. F. had been reported to occur in giant-cell arteritis. In five of the cases examined the C. S. F. showed mild pathological changes (Table 29). According to the laboratory the normal values for the protein content of cerebrospinal fluid obtained by lumbar puncture are 0—65 mg/100 ml for males, and 20—50 mg/100 ml for females. Case 15 had loss of tendon reflexes in lower limbs, case 65 (*vide infra*) developed hypopituitarism and case 93 had an aortic arch syndrome.

HYPOPITUITARISM PROBABLY DUE TO PITUITARY INFARCTION

One patient in series B developed hypopituitarism.

Case 65 G. Ö. — The patient, a 60-year-old man had developed slowly progressive bilateral shoulder periarthritis in 1963 and the E. S. R. rose to 96 mm/1 h. After a remission he became worse 1 year later and in December 1964 he had a complete polymyalgic syndrome. The patient was not seen again until 1 year later by which time he had undergone a remarkable change. He himself complained only of moderate rheumatic symptoms, but the signs of hypopituitarism which had developed in the meantime were obvious. The skin was pale, dry and thin. Most striking was the loss of previously strong hair growth on the chest and very severe reduction of axillary and pubic hair. The prostate was small and the testes were atrophic. Beard growth had decreased considerably. He had lost libido and sexual potency. The blood pressure in the arms was 90/60 mm Hg. The pulse in the temporal arteries could sometimes not be palpated with certainty. No defect of the field of vision could be demonstrated. Tomography and lumbar encephalography revealed no signs of an expanding process in the base of the skull.

In April 1966 examination revealed pleocytosis which had disappeared 20 months later (Table 29). BMR, PBI, ACTH-loading with determination of total number of eosinophilic leucocytes, 17-ketosteroids and 17-ketogenic steroids and the result of the metopirone test were compatible with the diagnosis of hypopituitarism. He was given substitution therapy with thyroid preparation and cortisone; the blood pressure then rose to 130/80 mm Hg. or more. He improved and could return to work, even heavy work as a forester after having had the disease for 4 years. Biopsy of temporal artery was negative at first occasion and produced no specimen at second attempt on the other side (Chapter 4).

SYMPTOMS AND SIGNS OF VISCERAL INVOLVEMENT

Impaired liver function

As mentioned in the beginning of this chapter the constellation of pruritus and impaired liver function without jaundice was observed in one of the earliest cases. This prompted a systematic investi-

gation of such symptoms and signs in patients and controls Pruritus was noted in 18 (24 /) of 76 *patients questioned Pathologically increased values* for serum G P T and/or alkaline phosphatase were found in 9 patients, 7 of which belonged to series A, but in none of the controls. These investigations will be reported elsewhere

Patients with gastro-intestinal symptoms

One patient (No 49) died from intestinal gangrene before planned biopsy had been performed One patient (No 43) died from acute pancreatitis. In both cases arteritis was diagnosed post mortem (Hamrin et al. 1968) Both patients had giant-cell arteritis in aorta and/or large arteries

Aortalgia and cardiac symptoms

In PMA pain and tenderness to palpation may occur along large arteries, especially along the carotid arteries. It is presumably a phenomenon parallel to that of headache and pain along the temporal arteries on involvement of cranial arteries. Occasionally patients have chest pain, not elicited by physical exertion A typical case in this respect was No 19 *with an aortic* arch syndrome, mentioned in an earlier report (Hamrin et al. 1964). That the pain might be elicited in such cases by acute aortitis, an aortalgia, or by inflammation of the large arteries of the aortic arch should be considered as a differential diagnostic possibility in cases with obscure chest pain.

In case 43 (series A) clinical and electrocardiographic signs suggesting myocardial infarction were demonstrated on two occasions during the protracted course of the disease. The serum G O T was 50 U (Wróblewski) on the first occasion and 98 U on the second. In series B there was a similar case with a G O T of 52 U In 3 cases in series A without clinical symptoms or electrocardiographic changes suggesting myocardial infarction the values for G O T were found to be slightly increased. One patient in series B with normal transaminase values had AV-block grade I with varying conduction times for some weeks in the early stage of the disease

Patient No 6 died 3 years after the onset of PMA (published as case No 3 in Hamrin et al 1968). The *patient had advanced prostatic cancer* He died from pulmonary oedema, which occurred following severe fever after catheterization of the urinary bladder Post-mortem revealed, among other things, inflammatory changes in the right coronary artery and interstitial myocarditis with focal infiltrates resembling Aschoff bodies.

PAIRS OF SIBLINGS	CASE No.	AGE	SEX
I	54	70	♀
	77	70	♀
II	49	74	♀
	13	67	♀
III	71	70	♀
	84	70	♂
IV	28	58	♀
	8	54	♂

Fig. 13 Four pairs of siblings in the Växjö material which consisted of 93 cases of PMA. Cases belonging to series A are denoted by filled symbols, those belonging to series B by hollow symbols. The ages refer to age t onset.

FAMILIAL OCCURRENCE OF PMA

Though the patients were not questioned as to the occurrence of rheumatic diseases in the family the material included 4 pairs of siblings. In the siblings of pairs I and III (Fig. 13) the difference between them in age at onset was 5 months and 2 months, respectively In pairs I II and III the course of the disease was the same for both siblings, but differed considerably between the siblings in pair IV

The case reports of the two siblings in pair No I are given below

Case 54 A T (Fig. 14). — The patient was retired teacher She fell acutely ill on her birthday on 16 September 1964 with chills and influenza-like pain in the shoulders, upper arms, neck, hips and knees. The whole body was tender and stiff the following morning and she could barely manage to put on her clothes. For some time afterwards her life was miserable, she could, for example, only reach her apartment on the first floor by creeping on all fours. In January 1965

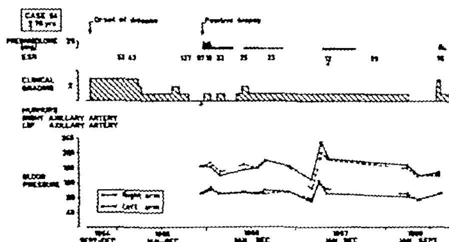


Fig. 14. Graphic demonstration of course in case 54. Clinical grading, as judged from intensity of pain and reduction of mobility essentially according to Gordon (1960). Grade 4 severe pain with reduced mobility of neck, shoulders and hips. Patient severely disabled. Grade 3 moderate pain with reduced mobility of at least one of these joints. Grade 2 mild, but constant, pain requiring continual use of analgesics. Grade 1 mild, inconstant pain requiring analgesics at most occasionally.
Symbols
↓ time of diagnosis; point denotes no murmur; unfilled circle, faint murmur (grade I); half-filled circle, loud murmur (grade II); and filled circle, loud murmur with frémissement (grade III).

she was referred to the dpt. of internal medicine under the diagnosis of "periarthritis and rheumatoid arthritis. She was then somewhat better. The diagnosis made was osteoarthritis deformans. Later she again had more severe pain in the shoulders, the left became "frozen" and pain also developed in the region of the left elbow. In the first half year of 1965 she had severe disturbance of the sense of taste: sugar tasted extremely sweet, coffee and tea, better. She also had pruritus on the back for a short time. During the first year of the disease she lost 14 kg.

In October 1965 she was again admitted to hospital. She was slightly febrile and the E. S. R. had risen to 127 mm/1 hr. Electrophoresis showed normal γ-globulin and markedly increased -globulin and reduction of the albumin fraction. The haemoglobin was 10.1 g/100 ml, R. B. C. 3.3 mill./µl and W. B. C. 4,300 per µl. The alkaline phosphatase was 9 U (Buch & Buch) and had earlier been 17 U. Systemic collagen disease was suspected.

When the patient attended the out-patient department in December 1965 she was accompanied by her year-younger sister (case 77 below), who had been a nurse. On critical analysis of the patient's history it was realised that the diagnosis might very well be PMA. In September 1965 the patient had transitory pain in the jaw joints and had noticed "something hard in the temples. Her sister the nurse had then observed "hard, tortuous blood vessels" in both temples. The vessels were not reddened and were not tender. At the visit in question 4 months later the sister observed that these arteries had "shrunk away". The temporal arteries were no longer visible. Pulsations could still be felt in the main trunk, but not further in the branches. A few weeks before this examination the patient had had swallowing discomfort. Biopsy specimen of the left temporal artery showed the picture of giant-cell arteritis.

One week after this visit arcuate flashes and sparkling occurred for 10 minutes before the left eye. Her vision that day was 0.8 on the right side and 0.9 on the left. Perimetry suggested bitemporal scotoma. The ocular fundi were sites of choroidal atrophy. The papillae were of normal appearance. Steroid therapy was started. During the following 2 weeks the patient had on 2 occasions a greyish shadow spreading outwards from the middle of the field of vision of the left eye. Brief episodes, a second or so long, of ocular sparkling occurred during the following year despite steroid therapy. Roentgen examination of the sella turcica and lumbar encephalography in 1966 because of the bitemporal scotomata revealed nothing remarkable.

The rheumatic symptoms regressed in the course of the following 3 years during which she received 5 cures with prednisolone. During tentative withdrawal of the treatment in August 1968 she had a severe attack of torticollis, and the E. S. R. rose to 75 mm/1 hr.

Arteries. The blood pressure in the arms was equal on both sides in December 1965 (Fig. 14). Murmurs of stenotic character were then heard over the left axillary and brachial arteries and 1 month later murmurs were also heard over the vessels in the right arm. In the

autumn of 1966 the patient reported paresthesia in the fingers of the left hand. When the arms were stretched pwards the left hand became paler than the right. Some months later severe pain occurred in the left arm and hand and the pulsation in the left radial artery felt much weaker than in the right. The blood pressure was then significantly (Chapter 10) lower in the left arm.

Case 77 E G — The patient was a sister of the one just described (No 54) Like her sister she had felt acutely ill in December 1966 with myalgia in the pelvic girdle and thighs and 1 month later also around the shoulders. On some occasions she was troubled by entoptic phenomena in the form of flashes and stars before the eyes. She suddenly became worse in February 1967 with severe pain and stiffness of the neck and fever (up to 38.8 C). On March she had stabbing pain from the neck radiating up behind the ears. The skull was tender and combing of the hair was painful. She was treated with penicillin which, however had no effect on her condition. On the 10th of March pain and swelling before the ears supervened, but no reddening was observed On March 18 a black shadow was drawn like a curtain from the side into the field of vision f the right eye. She realised that she was blind on her right eye She observed that 8 minutes later light slits, like windows, appeared in the field of vision of the blind eye and the blindness soon disappeared all together A roughly equal period of amaurosis fugax occurred on the same side 3 days later but this time the field f vision was not black, but dazzling white.

On March 29 the patient was admitted to Karlshamn hospital (Dr R. Nyström). The E. S. R. was 47 mm/1 hr Vision was 1.0 on both sides. The field of vision and the ocular fundi appeared normal. The temporal arteries seemed clinically normal but on the basis of the patient's history a diagnosis of temporal arteritis was made. Prednisolone was instituted in a dose of 30 mg per day which was reduced to 10 mg per day 6 weeks later Owing to occasional eye symptoms and transitory aphasia the patient was treated with a small dose of steroid during the following years.

Biopsy of the left temporal artery in May 1967 was technically difficult because the artery was embedded in adhesions. Histologic xamination of the specimen showed arteritis.

The course of the disease during the first year in the following case, No 28 (pair IV), was much the same as that of her brother (No 8), but then took a different turn Case 8 occupies a unique position in the material

Case 28 K J (Fig. 15). — This patient with psoriatic arthropathy was 58-yea -old woman. She had two spells of bilateral shoulder periarthritis one and two years, respectively before the disease in question. On both occasions she had been treated with steroids locally and had recovered. In March 1963 she suddenly fell ill with influenza-like pain, which soon became localised to the shoulders, hips, groins and thighs. She had paresthesia of the hands. She became stiffer and stiffer she could not get up in the morning or dress herself without help She lost 15 kg in the first year of the disease.

In 1963—1965 she was admitted 6 times to the dpt. of internal medicine. During intermittent withdrawal of steroid therapy in the course of these years the temperature rose to 38 °C and the E. S. R. was usually very high.

She was admitted to hospital for the first time in June 1963 Treatment with steroids resulted in improvement and recovery of full range of motion of the

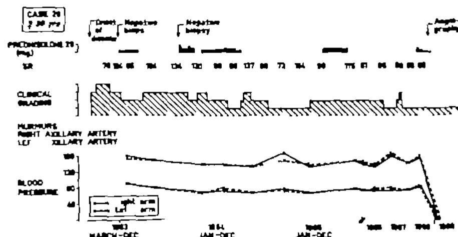


Fig. 15 Clinical course of case 28. For explanation of the diagram see Fig. 14





Fig. 16. Bilateral subclavian arteriography Contrast medium injected into aortic arch. Marked irregularities and narrowing f the subclavian and axillar arteries on both sides. The luminal reduction progresses distally and is most marked in the proximal part of the brachial artery On the right side the brachial artery appears to be completely occluded, the arm being supplied exclusively via wide collateral arteries. The most marked changes ppear bilaterally after the departure of the subscapular and posterior humeral circumflex arteries. (Case 28). (Cf. Fig. 28 Chapter 10).

shoulders. I the autumn of 1963 treatment was withdrawn and she became much worse.

From January to May 1964 she was again cared for at the department. During this time the disease progressed rapidly She presented the picture of frozen shoulder She walked with small shuffling steps. The ervical spine was also stiff. During this time she got severe dysgeusia all food, even sweet dishes, tasted salty and on several occasions she noticed that this disturbance of the sense of taste disappeared within a day as soon as prednisolone was instituted. She had *burning of the tongue. The tongue was red, smooth* and glossy She had not achylia. Hb 8.6 g/100 ml. R. B. C. 3.3 mill/μl. MCV 90 mpl MCHC 30.9 g/100 ml. W B. C. 12,600 total eosinophils 281 and later 556, and platelets 421,000 per μl. The folic acid content of the serum was abnormally low and the absorption of vitamin A was impaired. During treatment with folic acid and simultaneous slow regression f the disease the anaemia improved and the tongue papillae reappeared

She had not had temporal symptoms and the temporal arteries felt normal. Examination f biopsy specimen of the left temporal artery in June 1963 and of the right in February 1964 revealed nothing remarkable.

In February 1964 she became worse with increasing fever and swelling f the hands, which became stiff but not painful

The condition resembled a severe shoulder-hand yndrome During treatment with prednisolone the muscle pain disappeared and the range of motion of the large joints became normal, while the hands became steadily worse. Flexion deformity of the fingers developed Judging from the E. S. R., the disease at that time was very active, since despite steroid therapy she still was slightly febrile and the E. S. R. was more than 100 mm/1 hr

During the following 2 years the patient's polymyalgic symptoms disappeared completely The oedema of the hands gradually disappeared, leaving behind contraction processes in the palmar aponeurosis and contractures in the hands. After the hands had been *attacked in 1964 signs of dermatitis between dig. III* and IV on the left hand was observed. According to the dermatologist (Dr G Krook), there were typical psoriatic changes in the nail of the left thumb with distinct onycholysis. The cutaneous changes were clinically and histologically typical of pustular psoriasis. After she had had the disease for 5 years the function of the hands was severely limited. The range of motion of the wrists was reduced to 10—20 The fingers assumed the typical appearance f arthropathia psoriatica, which has been likened to sausage-fingers. Prednisolone was thus unable to prevent severe destructions of the hand and finger joints, whose gross and roentgenologic appearance were characteristic of arthropathia psoriatica.

Until the summer of 1968 no stenotic murmurs were heard over the arm arteries and the blood pressure was usually equal in both arms (Fig. 15). After 5 years disease the radial pulse could not be felt, the blood pressure could not be measured auscultatorily in either arm, and distinct murmur was heard over

both axillary arteries. Angiography of the brachiocephalic trunk and left subclavian artery showed severe stenoses bilaterally (Fig. 16).

DISCUSSION

PMA is a systemic disease involving the aorta, large arteries and arteries down to the calibre of roughly that of the temporal arteries. There might therefore be reason to expect a polymorphous flora of symptoms. It is not possible to secure statistical support for a causal relationship as regards symptoms with low frequency in PMA The less common a symptom or syndrome *per se* the more likely its occurrence in PMA is not simply due to chance. But also isolated observations of common, cryptogenetic conditions of probably varied aetiology are of interest. As a matter of fact, a number of symptoms and signs, often mild and transitory and some of them of low frequency have been reported in *pertinent compilations and surveys of giant*-cell arteritis (Cooke et al. 1946, Andersen 1947 Russell 1959 Hollenhorst et al. 1960 Baumann 1964 Andrews 1966, Hunder et al. 1969 and Hamilton et al. 1971) The review by Hamilton et al (1971) is very comprehensive

Neurologic symptoms — Disorders of gustatory and olfactory senses in PMA were first reported by Hamrin et al (1964). These symptoms have not received much attention by other authors. It is, however interesting to note that in one of the earliest and best described cases of temporal arteritis (Jennings 1938) "the food seemed dull and tasteless In this connection a recently described syndrome reported by Shafar (1965) and characterised by perversion of the sense of taste and loss of body weight and occurring in the aged may be of relevance Shafar suggested that the syndrome might be on a vascular basis, but did not consider the possibility of arteritis. The values for E. S. R. were not given in his report. Most of the patients in the present material were questioned regarding symptoms from the chemical senses so that the possibility of a suggestive effect cannot be excluded. But, then again, the reaction of the patients with such symptoms was convincing. One patient had such severe dysosmia that she first consulted an ear-nose-throat specialist Compared with other symptoms, however the disturbances of the senses of smell and tast were both mild and transient. The rapid and favourable effect of steroid therapy suggests that the disorders of the senses of taste and smell as well as the eye symptoms were due to an inflammation of the arteries supplying the tongue and the olfactory region in the nasal cavity Some patients also had other symptoms, which might be interpreted as manifestations of impaired supply of blood to the tongue. Thus, some patients had glossitis and some reported that their tongue felt swollen and funny" These symptoms are discussed further in association with similar observations made in the Malmö material of temporal arteritis (Chapter 12).

One patient had a peripheral facial paresis, which occurred early in the course of the disease A slight increase of the protein content of the C. S F was also noted Another patient had loss of the knee- and ankle jerks. *Bell's palsy* and *loss of tendon reflexes in the lower limbs* are signs not reported in the literature on temporal arteritis and PMA. Russell (1959), however reported 2 cases with mononeuritis (lateral popliteal palsy and median nerve lesion, respectively) in giant-cell arteritis and thought that the nervous symptoms might be due to ischaemia. Symptoms of polyneuritis in temporal arteritis have also been described (Meadows 1966 Warrell et al 1968)

Dizziness is a common symptom in cerebrovascular insufficiency It is often due to narrowing of the cervical parts of the carotid and/or vertebral arteries (Hutchinson & Yates 1957) According to these authors, stenosis of the vertebral artery in such cases is often confined to the departure of the vessel from the subclavian artery The possibility that such stenosis may be postarteritic should be borne in mind (cf case 83 in Chapter 7) In this connection it is of interest to note that dizziness in association with headache, neckpain visual disturbances and sometimes brachialgia has been described as an independent syndrome by Barré (1926), who ascribed the symptoms to compression of the vertebral artery in patients with cervical spondylosis. In some respects this syndrome clearly resembles the constellation of symptoms often seen in PMA

Changes of protein content of the cerebrospinal fluid were observed in 5 of 18 cases examined A considerable pleocytosis and a pathological increase of C S F protein were noted already by Gilmour (1941) in one of his cases. These findings might, of course, have been caused by a coincident virus infection In other cases on record only a mild *increase of the C S F protein* has been recorded

(Cooke et al. 1946 Russell 1959 Hamrin et al. 1964)

Hypopituitarism. — That the picture of hypopituitarism in case 65 was secondary to arteritis is suggested by the absence of any demonstrable intracranial tumour despite prolonged observation, the appearance of the symptoms during the course of polymyalgia, the absence of pulsations in the temporal arteries and the absence of a representative artery at the second attempt to obtain a biopsy specimen of the temporal artery despite careful exploration of the region Clinically hypopituitarism appears not to ha e been diagnosed in patients with temporal arteritis or PMA. Hypophyseal necrosis has, however been diagnosed post mortem in 2 cases of temporal arteritis (Gilmour 1941 Jennings 1948) and involvement of the anterior superior hypopyhseal artery was observed post mortem in a case of temporal arteritis (Crompton 1959)

Visceral involvement — As mentioned before findings indicating liver involvement will be published separately

One of the patients died from intestinal gangrene, but unfortunately neither the coeliac nor the mesenteric arteries were examined post mortem. Without any obvious relation to the clinical course Cooke et al. (1946) found inflammatory changes of the superior mesenteric artery in 2 cases of temporal arteritis at post-mortem Case 31 in Russell's paper (1959) was, however operated upon because of intestinal gangrene. The operative specimen in that case showed inflammatory changes of the superior mesenteric artery Cooke et al. stated as early as 1946 that "until many more autopsies have been carried out, little progress can be made Their postulation may still hold good to-day It is desirable that in such cases complete autopsy including an extensive examination of the visceral vessels, be performed by pathologists with a thorough knowledge of the clinical problems.

In the present material of PMA the frequency of cases with heart symptoms is probably not larger than what might be expected in an unselected population with this age distribution In some of the cases systolic murmurs ppeared over the aortic area or existing murmurs became more intense in the course of the disease Routine electrocardiography also sometimes showed abnormalities. The material was, however not examined closely from cardiological point of view It should also be emphasised that patients with symptoms of PMA were not included in the material if they presented coronary symptoms or myocardial infarction on arrival at hospital Fatal myocardial infarction ascribed post mortem to arteritis of the coronary arteries has been reported (Frangenheim 1951 Morrison & Abitol 1955 Wiedermann et al. 1958, Crompton 1959 Spencer & Hoyt 1960 and Harrison & Bevan 1967). Coronary arteritis has occasionally also been demonstrated post mortem in patients who had not died from myocardial infarction (Hamilton et al. 1971) In patients with myocardial infarction prolonged subfebrility and persistently high and possibly rising E. S. R. arteritis should be suspected as a cause of the infarction, as pointed out by Paulley and Hughes (1960) Such a cause of myocardial infarction should be particularly suspected in patients with co-existing symptoms of periarthritis.

In some of the present cases proteinuria with an abnormal urinary sediment, usually only transient, was observed during the active phase of the disease. These cases were, however not investigated systematically from a renal or urological point of view Such findings have been reported in polymyalgia rheumatica (Bagratuni 1956, Barber 1957) and in temporal arteritis (Oldberg 1942, Cooke et al. 1946, von Knorring 1966 and Meadows 1966). An interesting case of renal insufficiency in a patient with giant-cell arteritis has been described by Balmforth (1964) and will be commented upon further in Chapter 1_.

Neither was the material analysed with respect to the frequent blood-pressure determinations. In some cases there was a marked difference between the blood pressure in the arms and that in the legs, and in others arterial hypertension developed Only those cases with significant differences in blood pressure between the arms and those with a blood pressure too low to be measured in one or both arms are ccounted for in the chapter on aortic arch syndrome in PMA (Chapter 10)

Inheritable predisposition for PMA?

The material included 4 pairs of siblings. This is noteworthy because the patients were not questioned systematically concerning the existence of rheumatic diseases in the family It is remarkable that in 3 of the 4 pairs the course of the disease was similar in both sibs and that in all 4 pairs the onset of the disease occurred at the same age in each

pair The similarity in course of the disease is illustrated by the case reports of the 2 sisters in pair No I in which both had similar visual disturbances These sisters, like a brother and a sister (pair No III), were all 70 years old at the time of onset of the disease The difference between siblings in age at onset of disease in each of these two pairs was only a few months.

*Barber (1957), who suggested the name poly*myalgia rheumatica, founded his investigation on 1_ cases Two of these patients were sisters and they fell ill at 65 and 66 years of age, respectively The author has knowledge of 3 pairs of siblings with histologically verified temporal arteritis, who were cared for at two other hospitals in the south of Sweden in the 1960s. One of these pairs was treated at the dpt of internal medicine in Kalmar (Dr K. Gydell). The patients were 2 sisters who had signs of aortic arch syndrome, like one of the sisters in the present material (case 54) The other 2 pairs of siblings were cared for at the dpt. of in*ternal medicine in Borås (Dr O Forssman).*

Morbus Takayasu or "young female arteritis is a condition which seems to be closely related to giant-cell arteritis in PMA (Chapter 10) It is therefore of interest to note that morbus Takayasu was diagnosed in two sisters (Alonso 196) In these two sisters the diagnosis was made when the patients were 15 and 19 years old respectively The arteries were not examined histologically

In Russell's (1959) series of temporal arteritis one brother of a patient had gangrene in one leg One patient in the Malmö series of temporal arteritis (Chapter 12) had a brother who had several *years before his death from myocardial infarction* had peripheral gangrene in the lower and upper extremities, which required mutilating operations of the fingers, toes and finally of both legs. The patient died under the diagnosis of morbus Buerger The vessels were not examined histologically

Familial occurrence of PMA and temporal arteritis has thus been observed. It is noteworthy that both members of each pair of siblings fell ill at roughly the same time The possibility of a genetic factor deserves attention

Psoriatic arthropathy

For a long time the clinical picture of the sister in the fourth pair of siblings was equally characteristic of PMA as that of her brother In the sister (No 28) the disease was closely followed up for several years. Without any serious objections her disease might be classified in the following order as. bilateral humeroscapular periarthritis, shoulder-hand syndrome, polymyalgia rheumatica and psoriatic arthropathy The picture changed successively so that psoriatic arthropathy finally crystallised as the most adequate diagnosis. *The psoriatic changes of* the skin and nails were insignificant. Whether they appeared before or after the rheumatic symptoms *is not known After 5 years of the* disease the patient developed signs of aortic arch syndrome, and both radial arteries became pulseless. No evidence is available that the aortic arch syndrome was due to arteritis, but the angiograms suggested postarteritic changes.

Psoriatic arthropathy is now generally conceived as a clinical entity differing from seropositive rheumatoid arthritis, which may coexist with psoriasis (Huskisson 1967 Wilkinson 1968) However the existence of hereditary predisposition for psoriasis is now generally accepted, but the mode of inheritance is still obscure (Romanus 1945 Wilkinson 1968). Huskisson (1967) *characterises psoriasis* as a genetically determined disease affecting skin, nails and joints As previously mentioned, some observations suggest a hereditary predisposition also of PMA or temporal arteritis No cases of coexisting psoriatic arthropathy and aortic arch syndrome could be found in the literature. The combination in this case may be regarded as purely incidental but both conditions are uncommon. The possibility of psoriatic arthropathy being the cli*nical manifestation of two different genetic defects* should also be considered A systematic investigation, clinical and angiographic, of the arteries of the limbs also in their proximal course, in psoriatic arthropathy might prove rewarding

ARTERIAL MURMURS IN POLYMYALGIA ARTERITICA

INTRODUCTION

Clinical evidence of stenosis of a large artery in temporal arteritis was first reported by Jennings (1938). In the first of his two cases the systolic blood pressure in the left arm was 35 mm lower than that in the right one year after the onset of the disease. After a further half year the difference was still the same as before, and the left radial pulse was "very hard to feel. In Gilmour's (1941) 4 cases of what he called giant-cell chronic arteritis" and which were examined post mortem, the clinical information given is very scanty. The first of these four patients was a 23-year-old woman. She had had a rheumatic disease. In the terminal stage of the disease the blood pressure in the right arm was 160/130 mm/Hg on one occasion and 220/130 mm/Hg on another. Nothing is said about the blood pressure in the left arm, but the left radial pulse was "almost imperceptible. The patient died from a ruptured aneurysm of the right subclavian artery. Post-mortem examination revealed local narrowings of the carotids and of the left subclavian artery. The stenoses were severe and partly occlusive. In a further 2 of Gilmour's cases there was severe stenosis of large arteries branching from the aorta. The earliest literature on giant-cell arteritis thus contains reports of clinical and patho-anatomical observations of stenosing processes in large arteries.

Carlander (1961) reported 11 cases of anarthritic rheumatoid disease" from a Swedish hospital. On clinical grounds he thought that the disease was probably a manifestation of giant-cell arteritis. In one of the cases no pulsation could be felt over the brachial artery after the patient had recovered. This was probably the first published case of aortic arch syndrome in a patient with polymyalgia.

Also during the first years of the clinical investigation of the present material the author gave special attention to inspection and palpation of large arteries. The following arteries were regularly examined: temporal, radial, carotid, subclavian, axillary, brachial, femoral and popliteal. The blood pressure was examined in both arms at each examination. With increasing experience it was realised, however, that it was difficult to detect small differences in the strength of the pulse between symmetric arteries with certainty. Other examiners called fairly often arrived at different results.

Bed side examination of the patients was supplemented in the autumn of 1963 by auscultation of large arteries. Auscultation proved to be definitely preferable to palpation because it gave information over and above that obtained by palpation alone. Distinct and sometimes loud murmurs of stenotic character could thus sometimes be heard over arteries where palpation had revealed nothing of interest. Sometimes a murmur was audible only over one artery but not over the corresponding contralateral artery without any difference in strength between the pulsation of the vessels being palpable. Further, a vessel with a faint murmur could usually be clearly distinguished from a really silent vessel. From January 1964 all large arteries were auscultated systematically at every examination of the patients. Preliminary experience with auscultation of arteries in PMA was reported in 1965 (Hamrin et al.). The auscultatory findings of arterial murmurs in a case of PMA, which developed signs of aortic arch syndrome, substantially stimulated interest in auscultation of the vessels (Chapter 10).

MATERIAL

From January 1964 to the end of August 1968 auscultation of the arteries was included routinely in the examination of the patients. At the beginning of that period the material consisted of 33 patients, all still living at the time of the present investigation and available for further observation. In all of the 93 patients in the material the arteries were auscultated on at least one occasion.

Originally for comparison of the frequency of arterial murmurs a control series was collected. The members were selected according to certain criteria (Chapter 2). The control series consisted of 96 persons (Chapter 3).

METHODS

To obtain as much information as possible from auscultation it proved useful to palpate the course of the arteries before actual auscultation. In the

absence of palpable pulsation auscultation was performed along the normal courses of the vessels A binaural stethoscope was used provided with both a funnel and a membrane Auscultation was done mainly with the membrane because it reproduced best the relatively high-frequent stenotic murmurs.

The patient was examined lying on an examination table Auscultation was started after the patient had rested for at least 10 minutes. The head end of the examination sofa was elevated to the first notch, corresponding to about 15 The patient's head was resting on a pillow At auscultation of the neck vessels the patient s head was dorsiflexed so that the stethoscope could be placed along the neck vessels without difficulty The patient was not allowed to turn or bend the head to the side. Also the arm arteries were examined with the arms in only one position viz. with the upper arm abducted 60—70 Experience taught that at auscultation of the arm arteries it was most convenient for the examiner to stand beside the patient s head, facing the foot end of the examination table and supporting one foot on a stool. The patient s arm was then placed on the examiner's knee With this position the patient's arm was relaxed and available for comfortable examination of the vessels of the upper arm. This is easiest if the patient's forearm is at the same time somewhat supine.

The following arteries were auscultated bilaterally carotid artery subclavian artery axillary artery brachial artery femoral artery and popliteal artery

The carotid artery was auscultated over at least 3 levels, namely immediately close to the mandibular angle, over the bifurcation and somewhat proximal thereto The subcl vian artery was examined both immediately laterally to the sternocleidomastoidal muscle and further laterally near the acromioclavicular joint. The axillary artery was always auscultated at apex axillae and further distally The brachial artery was auscultated of 3 points, namely 1) immediately distally to the insertion of the pectoral muscle on the humerus, 2) over the midlevel of the upper arm, 3) immediately above the cubital fold. The external iliac artery was examined immediately above the inguinal ligament, and th femoral artery immediately below The auscultatory findings at these two points were referred to a single vessel, namely the femoral artery It is often difficult to palpate pulsation over the popliteal artery In such cases it is often possible to locate the vessel by pressing the stethoscope in different directions in the popliteal fossa until the compression produces an artificial murmur Once this has been produced the compression is reduced and the examiner listens for spontaneous murmurs.

On each side 6 arteries were auscultated over all together 13 different points. At each examination the examiner auscultated over 26 points.

Only murmurs over arteries with the character of a murmur were regarded as such, *i.e.* synchronous with the pulse and of a certain duration Only murmurs that were distinctly heard on gentle application of the membrane against the skin were accepted as such If a murmur was heard, the contralateral vessel was always examined for any such murmur and compared with it A murmur over the brachial artery was recorded as such only if it was audible also over the distal half of the upper arm.

The intensity of the murmurs was graded as follows

Grade I = faint murmur
Grade II = loud murmur
Grade III = loud murmur in association with frémissement

The transition between faint and loud murmur was, of course, d ffuse For a murmur to be regarded as loud it should be readily detected without searching for it, and its detection should not require adaption of the ear to it, i rt should not require any ability of tune in (Levine & Harvey 1959).

Every time the vessels were auscultated the heart was also examined physically If a cardiac murmur was detected, it was studied for its transmission to the *juxtacardial vessels* Here, juxtacardial vessels are to be understood as the large arterial branches of the aorta with an auscultation area corresponding to the lower half of the neck, the supraclavicular fossa and immediate infraclavicular area. As pointed out by Rennie et al. (1964) and others, no clinical sign or method is available by which one can with certainty distinguish between an autochthonous arterial murmur and a murmur transmitted from the heart. With some experience of auscultation of the arteries it appeared reasonable to distinguish three categories of murmurs over arteries 1) murmurs with the character of stenotic murmur *i.e.* due to structural changes, usually combined with narrowing of the lumen, 2) murmurs transmitted from the heart and 3) murmurs of uncertain origin, including probably innocent murmurs over juxtacardial arteries.

When planning auscultatory examination of the vessels attempts were made to distinguish between autochthonous arterial murmurs of pathologic significance, transmitted cardiac murmurs, and possibly physiological turbulence murmurs. The following criteria were used in the classification of a murmur as an arterial and probably pathologic (hereinafter called arterial murmur):

A. In the absence of murmurs over the heart all murmurs over arteries were accepted as arterial murmurs except faint murmurs over juxtacardial arteries.

B. In the presence of weak cardiac murmurs (grades 1—2 according to Levine & Harvey 1959) the same principles were applied as in point A.

C. Louder cardiac murmurs (grades 3—4 according to Levine) occurred in 10 patients and of grade 3 in 4 controls. These murmurs were transmitted out into the juxtacardial vessels and, in one patient with aortic stenosis, also out into the axillary arteries. A characteristic of the transmitted cardiac murmurs was that they became rapidly and continuously weaker in peripheral direction. These sounds were not accepted as arterial murmurs. In some of these the transmitted cardiac murmur disappeared or became weaker in peripheral direction and distally thereto a stronger murmur was again heard but of another character. Such a murmur was classified as an arterial murmur. In doubtful cases other factors were taken into account, such as difference in frequency or length from the cardiac murmur. In a few cases the arterial murmur occurred earlier in the course of the disease than the cardiac murmur and was then regarded as a true arterial murmur. Cardiac murmurs are transmitted to the right carotid artery more readily than to the left. When in doubt as to the true nature of murmur its localization to the right carotid artery was therefore considered as arguing for it being of cardiac origin and to the left, of vascular origin.

It is clear from the above observations that irrespective of presence or absence of a cardiac murmur weak murmurs over the juxtacardial arteries were not regarded as arterial murmurs. On the other hand, murmurs over these vessels that were classified as loud according to the author's grading, were regarded as arterial murmurs except in those cases with simultaneous loud cardiac murmurs (grades 3—4 according to Levine).

All the patients and controls were examined in the same examination room, which was well insulated and quiet. The examination table was placed with the head-end against a wall, so that the patient could be readily examined from either side. The examination was not started from any particular side but sometimes from the left, sometimes from the right. The blood pressure was always measured only with Hg-manometers in a first class condition.

Notes on the physical state of the heart, blood pressure measurements and the results of palpation and auscultation of the vessels were made on special forms.

Auscultatory observation period and frequency of auscultation

The auscultatory observation period is to be understood here as the observation period during which arteries were systematically auscultated. It varied between 0 and 56 months. For 5 patients it was less than 1 month, and for 5 longer than 4 years. Distributed according to duration of observation, the material increased by about 10 patients for every 6 months. For the cases in series A the mean value for the auscultatory observation period was 24.7 months (range 0—56) and for series B it was 25.6 months (range 0—53).

Ignoring examinations performed less than 1 month before the previous auscultation the number of examinations per patient varied from 1—18. The distribution of these observations was uneven because, from the point of view of auscultation, the material consisted of populations, *viz.* 33 patients in whom the disease had been diagnosed before introduction of systematic arterial auscultation, and 60 patients who were added after that time. The patients examined on relatively few occasions included some of the earliest ones and some of those in whom the condition was diagnosed during the two last years of collection of the material. Table 30 gives the frequencies of auscultatory examination of each of the 6 pairs of arteries. The caudal vessels were not examined quite so often as the brachiocervical vessels.

In the 96 controls the arteries were systematically auscultated twice at an interval of 13—30 months (mean 22.7 months) in 70 of the cases and at a 4 year interval in 1 while the remaining 25 cases were examined on one occasion only.

Arteries examined	Number of examinations with auscultation distributed according to vessels and series		
	A	B	Total
Brachiocervical	311 (56 .)	243 (44)	554 (100)
Carotid a.	311	243	554
Subclavian a.	317	246	563
Axillary a.	305	242	547
Brachial a.	310	243	553
Caudal			
Femoral a.	263 (57)	196 (43 .)	459 (100)
Popliteal a.	201 (55)	162 (45)	363 (100)

Table 30. Frequency of auscultation of the 6 pairs of arteries in 93 cases of PMA. The examinations are distributed among series A (51 cases) and series B (42 cases).

Summing up, no notable difference in auscultatory observation period or frequency of auscultation was found between the patients in series A and B. The frequency of auscultation was, however much lower in the controls than in the patients.

Comments

The development, intensity frequency and duration of an arterial murmur will depend on many factors, such as the degree, form and length of the constriction of the vessel and the velocity of the blood flow These and other factors are also of significance in the transmission of the murmurs. Only in a few cases has it hitherto been possible to compare the auscultatory findings with angiographic and pathological findings (cf Chapters 7 10 and Appendix).

Owing to the intimate topographic relationship between the juxtacardial arteries it is not always possible to assign a murmur to any particular one of these arteries with certainty

The subclavian artery axillary artery and brachial artery are segments of the same arterial trunk. For the following reasons, however these vessels were considered separate vessels from the point of view of auscultation. By suitable digital compression of the axillary artery against the humerus it is easy to provoke an artificial stenotic murmur When planning the auscultatory examination the author convinced himself, by repeated tests on healthy persons, that such a murmur was barely transmitted at all in proximal direction and at most 10 cm in distal direction The observation that an artifical murmur is transmitted only a relatively short distance in distal direction is in good agreement with experimental and clinical observations in homo (Edwards & Levine 1952) and with graphic recording of murmurs in dogs with experimental aortic stenosis (Baker et al. 1966). A further reason for separate recording of murmurs over the above mentioned 3 arterial trunks was knowledge that early pathological observations in cases of non-syphilitic aortitis and arteritis (Raeder & Harbitz 1926, Frövig & Löken 1951) and angiographic investigations of such cases (Birke et al. 1957 Burstein et al. 1957 Wickbom 1957) have shown that (post) arteritic stenoses are often long The author thought that arteritis in PMA is identical with, or closely related to, these diseases. In order to reduce the risk of murmur over a stenosed axillary artery being recorded more than once *viz.* as a murmur over the axillary artery and as a transmitted murmur over the brachial artery a murmur over the latter vessel was, as previously mentioned, noted as such only if it was audible also over the distal half of the upper arm. Acceptance of the subclavian, axillary and brachial arteries as separate arteries from an auscultatory point of view nevertheless surely implies a certain overestimation of the number of murmurs if the occurrence of murmurs over these 3 arteries on the same side are ascribed to a corresponding number of stenosed parts. The frequency of murmurs over the arteries selected for auscultation must therefore be regarded only as a crude measure of a general tendency to stenosis and not as a measure of the frequency of anatomically well defined stenosis.

RESULTS

Despite endeavours to record only murmurs believed to be due to stenosis or structural changes of the underlying arteries the clinical significance

of arterial murmurs must be regarded as fairly uncertain. Therefore, strictly speaking, the following presentation is only an account of an analysis of acoustic phenomena heard along certain arteries.

An account will first be given of the auscultatory findings in patients and controls. Since these groups differed widely from one another in frequency of examinations, the findings recorded are not strictly comparable. With correction for these differences a comparative analysis will (see below) also be given concerning the frequency and various properties of the murmurs between patients and controls.

Auscultatory findings in patients

During the auscultatory observation period arterial murmurs were heard over one or more arteries in 55 (59 %) of the 93 patients. 49 % of the males and 67 % of the females had arterial murmurs. This difference with sex was not significant. Of the 51 patients in series A, 69 % had arterial murmurs compared with 48 % of the 42 patients in series B. This difference between the series was significant ($p < 0.05$). In each series there were relatively more women than men with murmurs, but in neither series was the difference significant.

The mean auscultatory observation period of patients with murmurs was 25.9 months in series A and 28.4 months in series B. For patients without murmurs the corresponding values were 21.9 in series A and 22.6 months in series B. The average number of times the patients with murmurs was auscultated was 7.0 in series A and 6.6 in series B. The corresponding means for patients without murmurs were 4.6 in series A and 5.5 in series B. The average duration of the auscultatory observation time was thus shorter and the number of auscultations per patient was somewhat smaller for patients without murmurs than for those with. The patients with murmurs were uniformly distributed among the age classes (Fig. 17).

Auscultatory findings in controls

Of the 96 controls, 15 (16 %) had arterial murmurs (Fig. 17). Such murmurs were heard in 11 of the men and 20 % of the women. This sex difference was not significant.

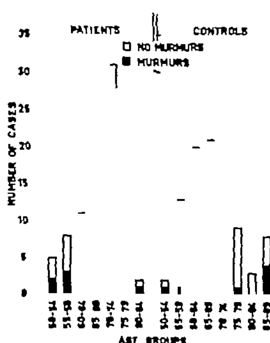


Fig. 17. Age distribution of 93 patients and of 96 controls with PMA with and without arterial murmurs.

Frequency of murmurs over individual arteries in patients and controls

It is clear from Table 31 that one third of the patients had murmurs over the axillary artery and equally many over the brachial artery. Almost as many had murmurs over the carotid artery. The number of murmurs over the subclavian artery was substantially lower. It should be observed that murmurs over this artery were accepted as such only if they were loud. In the arms bilateral murmurs were twice as common as unilateral murmurs.

Every tenth control had a murmur over the carotid artery. The frequency over leg arteries was lower. No murmurs were heard over the arm arteries.

Multiple occurrence of arterial murmurs in patients

Multiple murmurs were common in PMA (Table 32). One patient in series A had murmurs over 10 out of 12 arteries examined, and one in series B, over 9 arteries. The tendency to multiple murmurs was greater in series A than in series B.

	Auscultated arteries	No. of cases with bruits over different arteries			
		Unilateral occurrence		Bilateral occurrence	Total
		Dx.	Sin.		
Patients	A. carotis	5	14	8	27
	— subclavia	3	8	5	16
	— axillaris	3	7	21	31
	— brachialis	4	7	20	31
	— femoralis	6	4	7	17
	— poplitea	3	4	2	9
Controls	A. carotis	4	3	2	9
	— subclavia	0	1	0	1
	— axillaris	0	0	0	0
	— brachialis	0	0	0	0
	— femoralis	3	0	0	3
	— poplitea	2	3	0	5

Table 31. Number of cases with murmurs over various arteries in 93 cases of PMA and 96 controls.

Auscultatory findings over individual arteries in patients with arterial murmurs

Patients with unilateral or bilateral murmurs over individual arteries are surveyed in Figs. 18—23. In each case the upper mark denotes the right side, the lower the left. At most one auscultatory examination per month per patient is accounted for. Both the occurrence and absence of murmurs and the strength of murmurs are given in these figures. The cases are arranged according to the interval between onset and the first auscultation. As for the principal arteries to the upper extremities (Figs. 19—21) the time of diagnosis of aortic arch syndrome is given in the 9 cases in series A in which signs of the syndrome appeared with certainty after onset of PMA (cf. Chapter 10). It is clear from the figures that most of the patients were auscultated for the first time within the first 16 months of the disease. In a few cases auscultation was not started until the 28th month of the disease or still later. The patients who were not auscultated until late in the course consisted mainly of patients in whom the disease was diagnosed before 1964, when systematic auscultation of the arteries was started.

Seven patients with murmurs over the carotid artery (Fig. 18) and 6 with murmurs over the axillary artery (Fig. 20) were auscultated for the first time during the first half year of their disease. On that occasion none was found to have murmurs. Nine patients with murmurs over the brachial artery (Fig. 21) were auscultated for the first time within the first half year of the disease and in 2 of them (Nos *31* and *38*) murmurs were heard over

Table 32. Distribution of 93 patients with PMA according to number of arterial murmurs.

		Number of arteries with murmur											
		0	1	2	3	4	5	6	7	8	9	10	
Number of patients	Group A	16	8	2	5	8	4	4	1	1	1	1	51
	Group B	22	5	6	4	3	0	0	1	0	1	0	42
		38	13	8	9	11	4	4	2	1	2	1	93

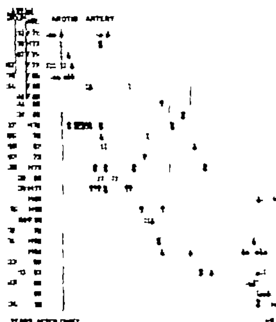


Fig. 18. Repeated recording of auscultatory findings in patients with a murmur over the carotid artery. Such murmurs were heard in 27 (8 men and 19 women) of 93 patients with PMA. For examinations performed more than 5 years after onset, the time of the last examination is given in the last column in months after onset.

Each symbol in the upper row denotes the right side, in the lower row the left side, of a patient. See also text.

Symbols
Point denotes no murmur
Circle faint murmur (grade I)
Half filled circle loud murmur (grade II)
Filled circle loud murmur with frémissement (grade III)
Arrow in Figs. 19—21 indicates time for first sign of development of aortic arch syndrome (Chapter 10)

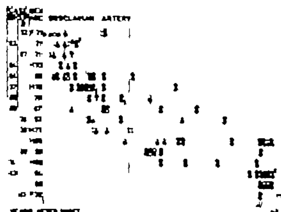


Fig. 19. Repeated recording of auscultatory findings over subclavian artery. Murmurs over this vessel were accepted as arterial murmurs only if they were loud (grades II and III). Of 93 patients with PMA 16 (5 men and 11 women) had murmurs of grade II or III over this vessel.
For explanation of symbols see Fig. 18 and text.

the brachial artery at the first examination. One (N 38) of them had, however, very probably had an attack of the disease long before the episode under consideration. It is clear from the figures that the frequency of murmurs at first auscultation over the above mentioned arteries was much higher when the examination took place later in the course of the disease. It is, however, also clear that the arterial murmurs sometimes develop already within the first half year of the disease.

Case No 82 was very informative in this respect. In that case the murmur occurred in the axillary and brachial arteries in the fifth month of the disease. The patient had then been in hospital for a few months and was being examined at short in-

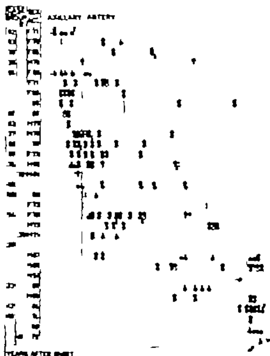


Fig. 20. Repeated recording of auscultatory findings in patients with arterial murmurs over axillary artery. Of 93 patients with PMA 31 (11 men and 20 women) had murmurs over this vessel. See also text and explanation of symbols in Fig. 18.

tervals In that case it was possible to determine with an accuracy of two weeks the time of development of the arterial murmurs in the arms (see also Chapter 10)

Constancy of murmurs

An arterial murmur was recorded as such either at the first examination or later during the observation period In both cases the murmur was heard at every later examination or it disappeared temporarily or definitively The arterial murmurs were thus either constant or inconstant If one defines such murmurs as constant as were heard at the two last examinations, and the others as inconstant, it will be found that 91 murmurs in the patients were constant and 103 inconstant. However some of the murmurs recorded as inconstant had probably disappeared as a consequence of obliteration or obturation of arteries. This occurred in some of the cases in which aortic arch syndrome developed during the disease

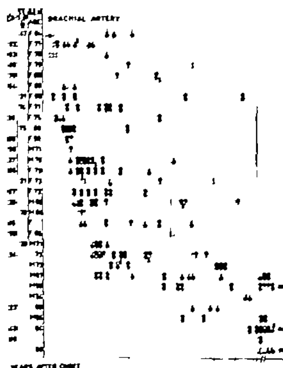


Fig. 21. Repeated recording of auscultatory findings in patients with arterial murmurs over brachial artery Of 93 patients with PMA, 31 (10 men and 21 women) had murmurs over this vessel. See also text and explanation of symbols in Fig. 18

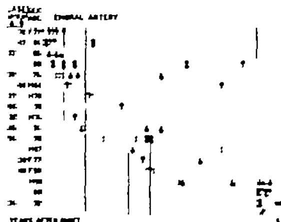


Fig. 22. Repeated recording of auscultatory findings in patients with arterial murmurs over femoral artery Of 93 patients with PMA, 17 (5 men and 12 women) had murmurs over the femoral artery
See text and explanation of symbols in Fig. 18

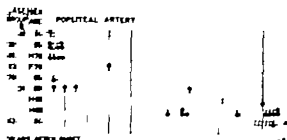


Fig. 23 Repeated recording of auscultatory findings in patients with arterial murmurs over popliteal artery Of 93 patients with PMA, 9 (3 men and 6 women) had murmurs over the popliteal artery
See also text and explanation of symbols in Fig. 18

The murmurs were constant in 52 % of series A and 35 % of series B The difference was significant ($p < 0.05$)

Of the 96 controls, 71 were examined twice and in these 13 arterial murmurs were heard. Only 2 of these murmurs were heard on both occasions.

Frequency of murmurs and their distribution among different arteries in patients and controls

All together 1 116 arteries were auscultated in the patients and 1 152 in the control series. During the observation period murmurs were heard over 194 of the arteries (137 in series A and 57 in series B)

In the controls the frequency of arterial murmurs was low The distribution of vascular murmurs among the patients and controls is given in Fig. 24

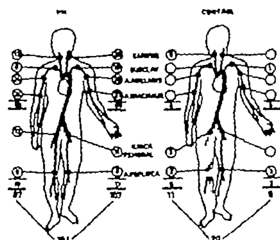


Fig. 24. Sites and frequencies of arterial murmurs recorded in patients with PMA and in controls.

Intensity of murmurs

The intensity of the arterial murmurs sometimes remained unchanged and sometimes varied during the observation period (Fig 18—23). At least on one occasion in the course of the disease 106 (55 %) of the 194 murmurs heard were loud (grades II and III). Loud murmurs over the axillary and brachial arteries were twice as common as weak ones Over 19 arteries (axillary and brachial arteries in 8 cases, and subclavian in 3) a loud murmur was accompanied by a frémissement (grade III).

Of the 20 murmurs in the control material 19 were classified as faint (grade I) and 1 as loud (grade II)

Left sided preponderance of murmurs

Murmurs over the brachiocervical arteries were more common on the left side than on the right (Fig 24 and Table 33). The difference was numerically small. If an arterial murmur is a manifestation of a pathological vascular process, it would be of interest to try to find out whether the sound occurs earlier on one side than on the other If a murmur appears earlier in the course of the disease on one side than on the other it could be taken as a sign of an increased vulnerability of the former vessel As far as the brachiocervical vessels concerned, unilateral cases were predominantly leftsided, and of bilateral cases in which the murmurs did not appear simultaneously the majority developed first on the left side (Table 33). The

Auscultated arteries	Number of cases with bruits recorded			
	only on one side Dx./Sin.	first on one side Dx./Sin.	only or first on one side Dx./Sin.	bilaterally when first heard
A carotis	5 14	1/0	6/14	7
— subclavia	3/8	2/2	5/10	1
— axillaris	3/7	0 3	3/12	16
— brachialis	4/7	0/9	4/16	11
— femoralis	6/4	1/1	7/5	5
— poplitea	3/4	0/1	3 5	1

Table 33 Survey of cases in which murmurs occurred first on one side or only on one side.

greater vulnerability on the left side suggested by these observations will be discussed in the next chapter on the aortic arch syndrome.

COMPARISON OF FREQUENCY OF MURMURS IN PATIENTS AND IN CONTROLS

This comparison was based on one auscultation per individual. In the controls it was the first, and sometimes the only examination. For the patients the values were arbitrarily chosen from an examination performed in the 18th month of the disease (Fig 18—23) or if no examination had been performed then the examination closest to that time It was found that 131 arterial murmurs had been heard in the patients. (A corresponding calculation for the 24th month of the disease gave 121 murmurs When the first or last examination in each case was used, the figures were 93 and 121 respectively The lower figure for the first examination reflects the fact that relatively many murmurs appeared during the observation period)

All together 14 arterial murmurs were found in the controls at the first examination

At the arbitrarily chosen time, i in the 18th month of the disease, 44 (47 %) of the 93 patients had arterial murmurs, compared with 10 (10 %) of the 96 controls (Table 34) According to this calculation, 59 % of the patients in series A had murmurs. The difference in frequency of murmurs between series A and the controls was significant ($p < 0.001$) In series B 33 % of the patients had murmurs. This frequency differs from that in the controls ($p < 0.01$). Also between series A and B the difference in frequency of cases with murmurs was significant ($p < 0.05$).

Series	Sex	No. of cases	No. of cases with arterial bruits	No. of cases without arterial bruits
A	Males	25	13	12
	Females	26	17	9
	Total	51	30	21
	%		59	41
B	Males	14	3	11
	Females	28	11	17
	Total	42	14	28
	%		33	67
A+B	Males	39	16	23
	Females	54	28	26
	Total	93	44	49
	%		47	53
Controls	Males	45	4	41
	Females	51	6	45
	Total	96	10	86
	%		10	90

Table 34. Comparison between frequency of cases with arterial murmur in 93 cases of PMA, distributed between series A and B and in 96 controls. The frequencies are based on a single examination in each case (see text).

At the same arbitrarily selected time, i.e. about 18 months after onset of the disease, murmurs were heard over 131 arteries — over 97 vessels in series A and over 34 in series B. Murmurs were heard over 16 % of the auscultated arteries in series A, over 7 % in series B and over 1 % in the controls. Using chi-test the differences were significant at a statistical level of $p < 0.001$ between series A and controls, series B and controls, and also between series A and B.

In the description of the total frequency of arterial murmurs in the patients at the end of the observation period it was pointed out that multiple murmurs were common in the patients (Table 32). Basing the calculation on a single examination in each case as before, i.e. for the patients about 18 months after onset of disease and for the controls the first examination, 25 (49 %) patients in series A, 8 (19 %) in series B and 3 (3 %) in the controls had 2 or more murmurs per individual. Distributing the cases into two groups, one with 0—1 murmur and one with 2 or more murmurs per individual, the differences were significant using chi-test between series A and controls ($p < 0.001$), between series B and controls ($p < 0.01$), and between series A and B ($p < 0.01$).

MURMURS OVER MAIN ARTERIES TO THE UPPER LIMBS

Murmurs over the main arteries to the upper limbs are common in PMA (Table 31 and Fig. 24). Murmurs were thus heard over the axillary and/or brachial artery in 34 patients, i.e. more than one third, but in none of the 96 controls. Half (25 of 51) of the patients in series A had murmurs over these arteries. The same was true for 9 (21 %) of the 42 patients in series B. This difference between the series was significant ($p < 0.01$). Such murmurs were heard in 9 (36 %) of 25 men and 16 (62 %) of 26 women in series A. This difference with sex is not significant. In series B the frequency was the same in both sexes.

When the frequency of patients with murmurs over the axillary and brachial artery was based on only 1 examination per patient, and then in about the 18th month of the disease, the frequencies were insignificantly lower (Table 35). Principally the distribution was the same with relatively more patients with murmurs in the arms in series A than in series B and with a significant difference at the level $p < 0.01$. Of the patients with murmurs in the arms, the murmurs were bilateral in 61 % in series A and in 43 % in series B.

DISCUSSION

Development of murmurs

On theoretical and experimental grounds Bruns (1959) criticised earlier theories on the development of cardiovascular murmurs, especially the classical turbulence theory. He presented a general theory of the production of cardiovascular murmurs which seems to have been widely accepted. He produced experimental support for his theory which he called the vortex shedding theory.

The vortex shedding theory has the advantage that it provides a uniform explanation for several characteristic features of murmurs in the clinic, viz.

Arteries with murmurs	Number of cases with murmurs over the main rteries to th upper limbs				
	Series A		*Series B*		*Controls*
	n=51		=42		=96
	Men =25	Women n=26	Men n=14	Women n=28	Men=45 Women=51
Axillary and brachial (4)	4	6	0	3	0
Idem (3)	1	3	0	0	0
Idem (2)	2	4	1	1	0
Axillary only (1)	1	1	0	1	0
Brachial only (1)	0	1	0	1	0
Total	8	15	1	6	0
Total (men and women)	23		7		0

Table 35 Frequency of cases with arterial murmurs over the main arteries to the upper limbs in patients and in controls based on one examination per individual. The figures in brackets give the number of arteries with murmurs over respectively 4 and 2 possible arteries.

a) the magnitude of the acoustic energy of the murmurs depends on almost periodical oscillations downstream of an obstacle·

b) the vast majority of murmurs are caused by protuberances of small or moderate size and by discontinuity in the heart, valves and large vessels

c) the intensity of the sound varies with the fourth power of the flow rate, i even very small increases in the flow rate cause disproportionately large increases in the intensity of the murmurs and

d) the murmurs are formed in the flowing blood and are transmitted peripherally via the myocardium and the vessel wall.

As for theories on the development of cardiovascular murmurs and their transmission, reference is made to Bruns (1959), McDonald (1960), Allen and Mustian (1962), Fuchs and Radloff (1962), Holldack and Wolf (1962), von Gierke (1960) and Caceres and Perry (1967).

Clinical evaluation of murmurs over arteries

Peart and Rob (1960) are surely right when they state that the art of auscultation was at its zenith about generation ago and that its importance has since decreased owing to advances made in diagnostic roentgenology As for auscultation of peripheral vessels, they thought that this is no longer widely practised except concerning vessels near the heart, and at examination for aneurysms and arteriovenous fistulae. Bühler et al. (1968) stated that only "a few enthusiasts now systematically auscultate peripheral arteries.

In recent years, however an increasing interest has developed in the auscultation of peripheral arteries as a screening method for arterial stenosis This may perhaps be explained mainly by the increasing use of angiography which has enabled comparison between acoustic findings and visual findings, by the role played by renal artery stenosis in the causation of arterial hypertension (Peart 1959) and by advances in vascular surgery (Rob 1959)

The vessels most often usculated are probably intracranial vessels and neck vessels, renal arteries and arteries supplying the lower limbs The commonest cause f stenotic murmurs is generally believed t be arteriosclerosis.

Auscultation of the skull has long been practised by neurologists (Mackenzie 1955). The discovery of the high frequency of progressive structural changes in the carotid arteries and their clinical significance in the development of cerebral ischaemic conditions (Hultquist 1942, Fischer 1951 1954) has stimulated interest in auscultation not only of the skull, but also of the neck (Fischer 1957 Crevasse & Logue 1958). Murmurs of the carotid artery are regarded as a reliable indicator of atherosclerotic plaques (Gilroy & Meyer 1962). Hammond and Eisinger (1962) stated that "the presence of a carotid bruit does not prove the presence of arterial disease, nor does the absence of such a bruit weigh heavily against the diagnosis. Rennie et al. (1964) shared this opinion, but thought that they had nevertheless obtained more positive in

formation in their material. Allen and Mustian (1962) stated that the clinical evaluation of a murmur over the cranium or in the neck is a complex problem and its interpretation in a given case is not always easy. They felt that the development of a murmur is not due entirely to structural changes in a vessel, but also to other conditions, such as anaemia and conditions with increased blood-flow possibly also to cerebral infarction and migraine. In a handbook on peripheral vascular diseases (Allen et al. 1962) is to be read "that rarely will a bruit be heard when the artery looks normal on arteriography and further that more than half of the significant lesions in the cervical portion of the carotid artery will be associated with a bruit of the bifurcation. This is in good agreement with observations made by Peart and Rob (1960).

Discussing arterial auscultation in general Peart and Rob (1960) stated "that the findings on auscultation of the peripheral artery system, when taken in conjunction with information obtained by a full clinical examination, can often enable the clinician to make an accurate diagnosis, and in many patients this single test may permit the omission of arteriography an expensive and time-consuming investigation, which is not always without risk. Fuchs and Radloff (1962) regarded auscultation of the vessels as a simple aid in the evaluation of the condition of the vessels but thought that the *findings were difficult to interpret. According to a* textbook by Holldack and Wolf (1962), murmurs do not normally occur over arteries at some distance from the heart and that a permanent murmur over a peripheral artery in a resting patient is a fairly certain sign of a stenosing process. Like Kappert (1964) they also felt that arterial murmurs are often an early symptom of a stenosis. Bühler et al. (1968) also believed that auscultation of peripheral arteries is a simple screening method for the early diagnosis of arterial stenosis, which is usually due to arteriosclerosis, and they felt that auscultation of peripheral arteries should be included in all physical examinations.

Opinions differ widely on the clinical value of arterial auscultation. These opinions are often carefully formulated and generally fairly positive. The uncertainty of the value of the examination is evidently due to insufficient knowledge of the structural and haemodynamic nature of the cause of development of vascular murmurs.

Earlier investigations

Interesting clinical observations have been reported in patients with vascular murmurs, and with the aid of modern techniques, particularly angiography arterial murmurs have been studied in detail in *single patients* or clinical *series of limited extent* (Myers et al. 1956, Fischer 1957 Crevasse & Logue 1958 Matthews 1961 Gilroy & Meyer 196.., Allen & Mustian 1962, Garrison et al. 1967). Most of these publications concern cervical and cephalic murmurs and Allen and Mustian's investigation is very comprehensive and thorough. The frequency of arterial murmurs over the carotid artery *in large series* has been systematically studied (Hammond & Eisinger 1962, Selvaag et al. 1968) and over this artery and several other arteries (Fuchs & Radloff 196.., Rennie et al. 1964). The auscultation findings have been compared with the arteriographic findings in the lower limbs in a large series of patients (Bühler et al. 1968).

Some of the above-mentioned investigations have the character of original clinical observations. Investigations of the frequency of murmurs over various arteries are relatively few and the results differ considerably between different authors. Thus, for example, Selvaag et al. (1968) found carotid murmurs in 5 % of middle-aged and elderly controls, while Rennie et al. (1964) gave 40 % for a series of roughly the same age distribution. Large differences between the results of *different investigations* are obviously due to differences in the criteria used for selection of the patients as well as to the auscultation technique and classification of arterial murmurs. Some authors recorded only what was regarded as "true stenotic murmurs while others accepted all murmurs along the carotid artery. A comparison of the frequencies of arterial murmurs found in the present material with those recorded in previous investigations would therefore be of dubious value. Such a comparison is also difficult because the present investigation of artery murmurs is a longterm follow-up study with frequently repeated examinations, in contrast with other investigations.

Murmurs over juxtacardial arteries

It is widely agreed that a murmur over a *peripheral artery* very probably indicates partial obstruction of the vessel in question provided that conditions with increased minute volume and flow rate can

be excluded g thyrotoxicosis, fever physical and mental stress and anaemia. Most authors do not give a precise definition of what they mean by peripheral arteries. In this connection it would appear appropriate to use the term to designate arteries which are not juxtacardial according to the definition given in this chapter

The clinical significance of murmurs over *juxtacardial arteries* is more uncertain than that of murmurs over peripheral arteries. A short systolic murmur of ejection type and of low or medium pitch over juxtacardial arteries has recently been discussed under the name of supraclavicular arterial bruit or carotid bruit in a monograph "The Innocent Murmur" (Caceres & Perry 1967).

This murmur is believed to be due to the turbulence at the departure of the large arterial trunks f om the aortic arch or at the division of the brachiocephalic trunk. This murmur which is conceived as innocent, is commonest in children and young persons. According to Caceres and Perry referred to above, it must be distinguished from murmurs of pathological significance in particular ly the following conditions

1) cardiac murmur (aortic stenosis, pulmonary stenosis and atrial septum defect),

2) arteriosclerotic stenosis of the brachiocephalic trunk, subclavian artery and carotid artery and

3) aortic arch syndrome

At least in somewhat elderly persons it is probably difficult to distinguish between such an innocent supraclavicular murmur and a pathological murmur in mild cases of the 3 conditions referred to above. Of particular interest in this expect is a postarteritic aortic arch syndrome, which is now being diagnosed more frequently and which, judging from the present investigation, is not uncommon. Fuchs and Radloff (1962) are also probably right when they suspect that owing to the relatively abrupt departure of the arteries from the aortic arch, even small changes at the origins of these branches are sufficient to disturb the lamellar flow of the blood and thereby give rise to a murmur They also belie that such changes may easily escape attention at autopsy Murmurs along carotid arteries and in the supraclavicular fossae may according to the experience of the present author be classified as follows.

1) T ansmitted cardiac murmurs

2) Clear stenotic murmurs. In typical cases the site of such murmurs are, strictly speaking, not juxtacardially but over the carotid bulb They are well demarcated and of medium or high pitch

3) Innocent murmurs are common in children and young persons. They are systolic murmurs of short duration and of low pitch and are situated over the juxtacardial arteries. Typical murmurs of this type correspond to the supraclavicular arterial bruit of Caceres and Perry (1967)

4) Murmurs of uncertain significance, *i. e.* murmurs over juxtacardial arteries in middle-aged and elderly persons and which naturally do not fall into one of the other categories. They may resemble supraclavicular bruit, but cannot be generally regarded as innocent. They are probably sometimes caused by arteriosclerotic or postarteritic changes at the departure of the large arteries from the aortic arch or somewhat distally thereto Postarteritic stenosis in elderly persons is probably more common than supposed. The sites of departure of the vessels from the aortic arch have not been studied angiographically so thoroughly as the carotid bifurcation and the internal carotid artery

Arterial murmurs in PMA

The method of selection of the controls implied a risk that some of these persons might have had PMA Despite endeavours to avoid this source of error which would tend to result in too high a frequency of murmurs in the controls, the possibility of such cases having been included must be realised. Also the design of the investigation is such that an unconscious bias on the part of the examiner cannot be excluded. As mentioned in the *description of the method*, no control was ever refused after auscultation of the arteries. It was also pointed out that it was not difficult to demonstrate or exclude the presence of murmur Though this does not exclude the possibility of over or under diagnosis of murmurs, this source of error was regarded as small.

According to the plan of the investigation arterial murmurs were recorded only if they satisfied certain criteria for autochthonous arterial murmurs of probably pathologic nature. The following reasons and observations suggest that the vast majority of the murmurs recorded were due to stenosing processes in the underlying arteries.

1) A priori the most reasonable explanation for the large difference in frequency of murmurs between patients and controls was the higher frequency of arterial stenosis among the patients

since severe stenosis was observed among the first published cases of temporal arteritis or giant-cell arteritis and since no other reason for this difference could be produced It is true that anaemia was more common and more pronounced among patients than among the controls, but is was never severe and can hardly have played more than a minor role. Only 4 of the patients had a haematocrit below 30 % and only 1 below 25 %. The patients had never had anaemia for a long time

2) It is clear from Figs. 19—21 that 9 (18 %) of the 51 patients with certain arteritis developed signs of aortic arch syndrome Anisosphygmia of the main arteries to the arms or absence of pulse in both arms indicates severe stenosis, obliteration or occlusion of the subclavian artery and/or axillary brachial artery It is natural to imagine that these cases are extreme variants of much more common stenosis of mild or moderate severity The frequency of arterial murmurs should, as in the present investigation, therefore be much higher than that of arteries with such severe stenosis as to give rise to signs of aortic arch syndrome.

3) Selective unilateral or bilateral angiography of the subclavian artery was performed in 11 patients (18 arms) In all of these cases stenosis was confined to the subclavian, axillary and proximal part of the brachial artery The narrowing was most often strongest in the axillary artery and its junction with the brachial artery It was thought that the diagnostic murmurs recorded could be well explained by these stenoses. Examples of these investigations are given in association with some case reports in the next chapter (see also case reports in Chapters 7 and 8)

4) In a large number of cases the murmurs had demonstrably occurred for the first time during the disease and the observation period (Figs 18—23) Thus, about half of the recorded murmurs were not heard at the first examination As for the axillary artery (Fig 20), for example, of the 31 patients with murmurs over this artery no such murmurs were heard over 22 arteries in 17 cases at the first examination

5) In many of these cases with murmurs, which appeared during and after the more acute stage of the disease, the nature of the murmur changed during the observation period Faint murmurs in some cases occurred only occasionally or intermittently In other cases a murmur was heard at every subsequent examination. In such cases it often in-

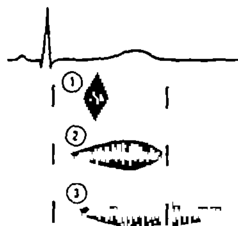


Fig. 25 Schematic illustration of three different types of vascular murmurs recorded from the axillary artery corresponding to increasing severity of arterial stenosis (1—3) 1 short systolic murmur 2 long and late systolic murmur 3 systo-diastolic murmur (cf. Hamrin & Thulesius, 1970).

creased in intensity became longer and of higher frequency Such changes also occurred in murmurs heard already at the first examination. Illustrative examples of changing character of murmurs over the arm rteries (Figs. 20—21) were Nos 1 37 66 70 82 and 83 over the carotid artery No 29 and over the popliteal artery No 7 Three characteristic types of arterial murmurs are illustrated in Fig. 25

6) In some cases frémissement occurred over the axillary artery or brachial artery during the observation period, sometimes soon after the appearance of significant differences in blood pressure between the arms, such as in Nos37 and 66 (Figs. 20—21) or No 43 (Fig 19)

7) With the gradual availability of post-mortem material it has been possible in a few cases to confirm the arterial stenoses both in cases where angiography had been performed and where it had not (Appendix).

The frequency of arterial murmurs in patients was lower over the vessels to the lower extremity than over the brachiocervical vessels. The following explanations may be offered for this uneven distribution

1) Arteries to the legs were examined less often than others.

2) It is not so easy to auscultate the femoral ar

tery and popliteal artery as other vessels studied. The popliteal artery like the femoral artery — except for a short part in the groin — lies deep in the soft tissues and especially the fatty tissue is a poor conductor of sound (von Gierke 1960)

3) The arteritic process may be less intense and less extensive in the lower half of the body than in the upper Information on the distribution of giant cell arteritis among various vascular territories of quantitative nature is scanty and does not warrant any conclusions. In so far as the rheumatic symptoms may reflect the extent and intensity of arteri tic processes the distribution and severity of those symptoms suggest a milder involvement of arte ries in the lower half of the body than in brachiocephalic regions (cf Chapter 7).

The lower frequency of murmurs in series B compared with that in series A may be explained by the following factors

1) Misdiagnosis. This possibility has been discussed previously and has been judged as probable in at most a few cases in series B (Chapter 7).

2) A milder course, on the average, in series B than in series A The mean of the highest E. S. R. was somewhat lower in series B than in series A, but the difference was not significant. As a support for the assumption that the E. S. R. is positively correlated with the severity of the disease, it might be mentioned that the E S R was significantly higher in 11 cases of aortic arch syndrome with histologically verified arteritis than in the other cases of arteritis ($p < 0.05$) But, on the other hand, there was no simple relation between the severity of the disease, as judged from E. S. R., and the occurrence of arterial murmurs since some of the cases that were most severe and had been followed up for longest time in series A (cases Nos 3 5 6, 18 and 25) had no arterial murmurs.

3) Effect of localisation of the arteritic process After a long observation period the patients were divided into two groups (A and B) according to the findings at microscopical examination of arteries Since the time of biopsy was determined to a certain extent by symptoms and signs from cranial arteries, there is reason to assume that the inflammation was confined to the aorta and the most central parts of the arteries branching from it more often in series B than in series A.

In conclusion, all of these factors probably contributed to the lower frequency of murmurs in series B and probably the factor discussed under point 3 was the most important.

It is also of interest to note that in both groups of patients the frequency of cases with murmurs, with multiple murmurs and with murmurs over the arteries to the upper limbs was higher in the women than in the men, but in none of these respects was the difference with sex statistically significant.

Murmurs over the main arteries to the upper limbs and scapulohumeral periarthritis

Murmurs over the principal arteries to the shoulder regions and arms, usually bilaterally were heard in roughly every third patient. They were thus common in the patients but never occurred in any of the controls It is remarkable — also in view of the indirect measurement of the blood pressure — that the arms have not been systematically auscultated in any published investigation No other arteries of such a caliber are so superficial along such a long distance as the axillary brachial artery Especially if the arms are thin, these arterial murmurs like pericardial rubbing, appear to be close to the ear

It is astonishing that these arteries have not been the subject of more direct investigation in patients with scapulohumeral periarthritis (Duplay 1872), frozen shoulder (Codman 1934) or in diseases around the shoulder joint which are sometimes associated with periarticular deposits of calcium salts and generally known under the name of painful shoulder" (Lancet 1953) or "stiff and painful shoulder It is obvious that PMA in almost all of these cases resembles those painful conditions of the shoulders (cf e case 15 in Chapter 7). The general symptoms in PMA are often brief or apt to be missed, and painful symptoms in regions other than the shoulder are usually milder and shorter than those around the shoulder The possibility of painful shoulder being of vascular origin appears to have been hardly discussed in representative and especially orthopaedic literature (Dickson & Crosby 1932, Codman 1934 Slocumb 1936, Withers 1949 Simmonds 1949 Lippmann 1951 DePalma 195., Lorenz & Musser 1952, Lancet (annotations) 1953 Moberg 1955 van der Korst et al. 1960 Kiami 196., Lidström 1963 Pinals & Short 1966, Moberg 1967 and Lundberg 1969). An exception to this rule are Sandström and Wahlgren (1937), who

found inflammatory changes in small arteries on histological examination of periarticular tissue from patients with periarthritis calcarea. They discussed the possibility of a vascular ischaemic origin of the disease, but apparently they did not examine the large arteries to the region of the shoulder (see also Sandström 1938 and 1939).

Internists in Europe have found shoulder periarthritis to be strikingly common in myocardial infarction. Scherf (1938) and Ask-Upmark (1944) described a syndrome in coronary insufficiency characterised by shoulder periarthritis in association with oedema of the fingers and infiltration of the palmar aponeurosis. Similar observations have been made in U.S.A. by Ernstene and Kinell (1940), and Askey (1941) described "the syndrome of painful disability of the shoulder and hand complicating coronary occlusion". The possibility of disseminated arteritis being the cause of this constellation of symptoms was not considered.

A similar syndrome of the shoulder and hand has been described by Steinbrocker (1947). Under the name of "shoulder hand syndrome" (Freyberg 1947) this symptom complex has become a fairly well established term (Graham & Rosen 1962). Steinbrocker (1969) has treated the syndrome in various papers and regarded it as a reflex neurovascular dystrophy of either idiopathic nature or elicited by a variety of diseases, such as myocardial infarction. Moberg (1955) stressed the role played by immobilisation in the development of oedema of the hand and fingers and suggested the name shoulder-hand finger syndrome. Though the syndrome has often been demonstrated in association with vascular insults of the brain and heart, the large arteries that supply the shoulder and arm have apparently not been systematically examined clinically, angiographically or patho-anatomically.

Arteriocirrhosis?

If it is true that most of the murmurs recorded in PMA patients really were due to arteritic or postarteritic stenosis one might wonder from a clinical point of view whether healed arteritis in PMA — a disease which is seldom fatal in the acute stage — might not produce an anatomic and histological picture difficult to distinguish from that of arteriosclerosis. It is generally accepted by pathologists that arteritis (cf. the syphilitic arteritis) precipitates arteriosclerosis. Idiopathic arteritis in PMA is evidently much more common than hitherto supposed. It is also not unlikely that the present material of PMA consists of relatively severe cases of a disease, which may thus be even more common. The idea that arteritis may produce arteriosclerosis also seems to be compatible with the hypothesis that a fair portion of the tissue changes in arteriosclerosis consists of postarteritic sclerotic parts. Without frequent examination during life and thorough knowledge of the clinical behaviour of the cases it appears likely that at least some of the cases in the present material of PMA, especially the cases of aortic arch syndrome, would have been classified post mortem as obliterating arteriosclerosis. Giant-cell arteritis is characterised histologically *inter alia* by destruction of the elastic tissue. The inflammatory infiltration is generally most severe in the media. It seems natural to imagine that the postarteritic, sclerotic and contracting processes in the media are more likely to cause stenosis and obliteration of the large arteries than subintimal lipoid deposits, degenerative changes and calcium deposits in the intima and inner parts of the media. Such a conception appears to be in good agreement with clinical, angiographic and with the patho-anatomic observations hitherto made in the present material of the polymyalgic disease. At any rate the pathogenesis of the stenosing and obliterating arteriosclerosis in large arteries appears to warrant a thorough study from this point of view by pathologists in intimate cooperation with clinicians.

In this connection it is interesting to note that Gilmour (1941), who suggested the name giant-cell chronic arteritis to designate cryptogenetic aortitis he described, wrote that "probably the effects of old aortitis in question have been seen but were regarded as arteriosclerotic or syphilitic." It would perhaps be justified to adopt the term *arteriocirrhosis* originally proposed by Nasu (1963) for the arteritis in Takayasu's disease, to describe the contracting process of the artery walls in PMA. This subject will also be discussed in next chapter which deals with aortic arch syndrome as a complication in PMA.

In connection with the above discussion it is of interest to refer to a study of the frequency of murmurs over large arteries in a large unselected material of in patients at a department of internal medicine (Fuchs & Radloff 1962). The higher age classes were predominant in a large material consisting of 1 000 patients. Attempts to correlate

the occurrence of the murmurs with arteriosclerotic diseases were not very rewarding. Thus, of patients with cardiovascular diseases, 27 / of the men and 37 / of the women had murmurs. The corresponding values for patients with *gastro-intestinal* and liver diseases were 30 / for the males and 39 / for the females. The material was therefore analysed in respect of parameters of arteriosclerosis (blood pressure ECG roentgenographically demonstrable calcium in the aorta, cholesterol values and changes in the ocular fundi). Only *for some of these parameters, and then only in the* higher age classes, was any statistical significance found at the 5 / level.

If, in accordance with the above hypothesis, postarteritic changes were the only cause of stenosis and obliteration of large arteries, arterial murmurs should never be heard in the control material. But such murmurs were heard, though not often. The murmurs in the controls were localised mainly to juxtacardial arteries and to the femoral artery and popliteal artery Only 1 of the 20 murmurs heard was classified (Fig. 24) as loud (grade II)

The murmurs over the carotid artery and subclavian artery may — as in a corresponding number of the patients — be of innocent character *i e* a supraclavicular arterial bruit according to Caceres and Perry (1967). This possibility can neither be confirmed nor refuted.

Mönckeberg's medial sclerosis has a predilection for the muscle arteries, and in particular in the lower limbs This special form of arteriosclerosis may perhaps explain some of the murmurs

It is also worth to recall that, according to the general theory of the production of murmurs set forth by Bruns (1959), even small or moderate *protuberances* and *deformities* of a vessel are capable of causing vascular murmurs, so perhaps an subintimal atheroma is enough to produce a murmur

A possible explanation for the murmurs in the controls or at least in some of them might also be that, as pointed out earlier they were false controls.

Summing up, the difference in frequency of murmurs in patients and controls was so large that it was well compatible with the hypothesis of postarteritic contraction processes, especially media, as the main cause of stenosis of large arteries.

CHAPTER 10

AORTIC ARCH SYNDROME

INTRODUCTION

The term *aortic arch syndrome* is here used to designate severe stenosis of one or more of the large arteries branching from the aortic arch. In the carotids the narrowing may be situated anywhere up to their entry into the base of the skull. In the arm arteries, down to the cubital fold. The diagnosis, then, did not require narrowing of an artery at its origin. Stenosis of a carotid artery was said to be present if its pulsation was absent or much weaker on one side than on the other. As for the arm arteries, the diagnosis was made if the blood pressure was too low to be measured in one or both arms or if the pressure on one side was significantly (≥ 25 mm Hg) lower in one arm than in the other. Such a difference was also invariably accompanied by a corresponding difference in the strength of the radial artery pulse. According to Sturm et al. (1970) such a difference in blood pressure is often a sign of disease.

Anisosphygmia of the radial arteries and a significant difference in blood pressure between the arms have been observed in a few of the earliest publications of cases of temporal arteritis and giant cell arteritis (Jennings 1938, Gilmour 1941). Therefore since 1961, when the first cases of PMA in the present investigation were diagnosed, physical examination always included measurement of the blood pressure in both arms. After two years we discovered the first case (No 19) with signs of aortic arch syndrome. In that case, which has been reported previously (Hamrin et al. 1964) the left radial pulse became much weaker during the spring of 1963 and the blood pressure in that arm fell. After the patient had had the disease for 10 months the blood pressure in the left arm could not be measured by auscultation or palpation.

Aortography of the left subclavian artery revealed a cornetshaped narrowing of the lumen of the axillary artery. Immediately after the departure of the posterior circumflex humeral artery the stenosis was almost occlusive. Further similar cases have since been observed.

This chapter gives an account of the cases of the aortic arch syndrome seen in the Växjö series of PMA.

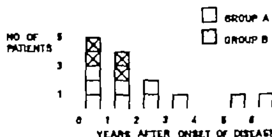


Fig. 26. Aortic arch syndrome in 14 (5 men and 9 women) of 93 patients with PMA. Patients distributed according to interval between onset of PMA and diagnosis of aortic arch syndrome. Cross in field denotes that the blood pressure was not measured bilaterally before appearance of aortic arch syndrome.

MATERIAL

In all of the cases the radial pulse was absent on one or both sides or the blood pressure was significantly lower on one side than on the other. As a rule, only the arm arteries were examined angiographically. Only cases with signs of aortic arch syndrome in the arterial trunks to the arms will be discussed here.

The material comprised 14 such cases (5 men and 9 women) with aortic arch syndrome (Fig. 26). Of these, 11 (5 men and 6 women) belonged to series A and 3 women to series B. The aortic arch syndrome was found in 22 % of the A-series and in 7 % of the B-series.

TIME RELATION BETWEEN ONSET OF AORTIC ARCH SYNDROME AND PMA

In 2 cases in series A and 2 in series B pulselessness or a significant difference in blood pressure between the two radial arteries was discovered during the polymyalgic disease, but since neither the blood pressure nor the radial pulse had been examined bilaterally before that time it is not known whether the aortic arch syndrome preceded PMA or *vice versa*. In Fig. 26 these cases are marked with a cross. In the remaining 10 cases the aortic

arch syndrome clearly appeared after the onset of polymyalgia. Nine of these patients (4 males and 5 females) belonged to series A, *i e* arteritis in these cases had also been verified histologically and 1 a female, to series B (No 28). Her case history is given in Chapter 8 because of the peculiar course of the disease.

Of the cases in which no definite time relation ship could be demonstrated between the onset of PMA and that of aortic arch syndrome, the syndrome was discovered within the first year of PMA in case 93 (series A) and in case 75 (series B) and *during the second year in case 41 (series B)* In case 34 (series A) it was 1 to 2 years, but this interval is uncertain because it was difficult to esti mate the time of onset of PMA

Of greater interest than these 4 cases are the other 10 cases in which the aortic arch syndrome was *discovered pro pectively* Six of the patients were women and 4 were men. The age at onset of PMA varied between 58 and 78 years. In 6 of these cases the onset of the aortic arch syndrome could be determined with an accuracy of one or a few months and in one case (No 82) to a time within period of 2 weeks. The syndrome appeared within 2 years of the onset of PMA in 5 cases and later in the other 5 (Fig 26) Nine of these cases belonged to series A. At the time when aortic arch syndrome was discovered a long time (10— 1 months) had elapsed since the preceding examina tion in 3 of these 9 cases, *viz.* Nos 1 35 and 70 *It is therefore possible that the aortic arch syndrome* appeared within 2 years in 7 of the cases in series A and later in 2.

*Fig 27 gives details about the auscultatory find*ings over the axillary and brachial arteries and about the signs of aortic arch syndrome in those 10 patients in whom these signs appeared with cer tainty after onset of PMA In the absence of mur murs at most one examination per month is given in the figure. For the sake of clarity the individual observations made after the appearance of mur murs and aortic arch syndrome are not marked in the figure. The interval between two consecutive observations was *at most 3 months in 78 / of* these cases. Three intervals were notably longer (19—25 months) *viz.* in cases 1 35 and 37 respectively It is clear from the figure that the blood pressure and pulse were examined bilaterally for the first time 1 and 2 months, respectively after

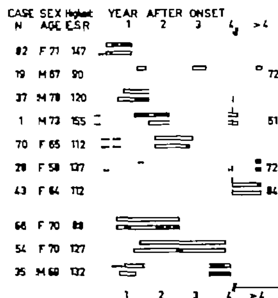


Fig. 27 Appearance f murmurs over axillary and bra chial arteries and signs of aortic arch syndrome in 10 patients with existing PMA. The upper horizontal in each case denotes right arm, the lower the left. Numerals in last column denote time of last observation in months after onset f disease. For explanations, see also text.

Symbols point denotes no murmur unfilled bar mur mur hatched bar blood pressure determinable by auscultation, but systolic pressure significantly (≥25 mm Hg) lower than in other arm and filled bar blood pressure not measurable by auscultation.

the onset of disease in 2 cases (Nos 1 and 8.) and *within the first year in 8 cases.*

The blood pressure in the arm could be measured by auscultation on only one side in 6 cases and on neither side in one case In some of these cases a weak radial pulse could be felt, but it was too weak to permit palpatory measurement of the blood pressure with anything like certainty

In cases 1 and 37 the blood pressure in one arm was too low to be measured for some months, but could afterwards be determined. After the end of the period covered by the present investigation the blood pressure has, however again become mea surable in cases 82, 19 and 70 But in the above 5 cases the systolic blood pressure then was 40—50 mm Hg lower in the worse arm *(i. e* the arm with the lower blood pressure). In patient 28 the blood *pressure again could be measured in both arms* and then no significant difference with side was found Patient 43 died soon after the aortic arch

CHAPTER 10

AORTIC ARCH SYNDROME

INTRODUCTION

The term *aortic arch syndrome* is here used to designate severe stenosis of one or more of the large arteries branching from the aortic arch. In the carotids the narrowing may be situated any where up to their entry into the base of the skull, in the arm arteries, down to the cubital fold. The diagnosis, then, did not require narrowing of an artery at its origin Stenosis of a carotid artery was said to be present if its pulsation was absent or much weaker on one side than on the other As for the arm arteries, the diagnosis was made if the blood pressure was too low to be measured in one or both arms or if the pressure on one side was significantly (≥25 mm Hg) lower in one arm than in the other Such a difference was also invariably accompanied by a corresponding difference in the strength of the radial artery pulse According to Sturm et al (1970) such a difference in blood pres sure is often a sign of disease.

Anisosphygmia of the radial arteries and a sig nificant difference in blood pressure between the arms have been observed in a few of the earliest publications of cases of temporal arteritis and giant cell arteritis (Jennings 1938 Gilmour 1941) There fore, since 1961 when the first cases of PMA in the present investigation were diagnosed, physical examination always included measurement of the blood pressure in both arms. After two years we discovered the first case (No 19) with signs of aor tic arch syndrome In that case, which has been reported previously (Hamrin et al. 1964) the left radial pulse became much weaker during the spring of 1963 and the blood pressure in that arm fell After the patient had had the disease for 10 months the blood pressure in the left arm could not be measured by auscultation or palpation

Aortography of the left subclavian artery reve aled a cornetshaped narrowing of the lumen of the axillary artery Immediately after the departure of the posterior circumflex humeral artery the stenosis was almost occlusive. Further similar cases have since been observed.

This chapter gives an account of the cases of the aortic arch syndrome seen in the Växjö series of PMA.

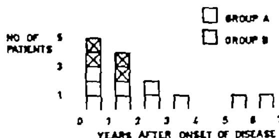


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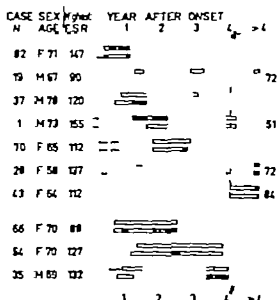


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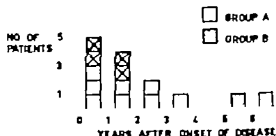


Fig. 6. Aortic arch syndrome in 14 (5 men and 9 women) of 93 patients with PMA. Patients distributed according to interval between onset of PMA and diagnosis of aortic arch syndrome. Cross in field denotes that the blood pressure was not measured bilaterally before appearance of aortic arch syndrome.

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Fig. 28. Normal appearance of left subclavian, axillary and proximal part of brachial arteries in patient examined by selective subclavian arteriography. Observe the smooth tapering of the arteries in distal direction and the appearance of the subscapular (arrow) and posterior humeral circumflex artery (arrow).

teria for frozen shoulder during part of their diseases (Table 36). Of these, Nos 28, 35 43 and 54 had a shoulder-hand syndrome for a varying period (Steinbrocker et al. 1948).

Temporal symptoms and signs were noted roughly just often as in the other cases as were disturbances of the senses of smell and taste (Table 36).

Paresthesia of the hands and Raynaud-like phenomena occurred in 9 of the aortic arch cases. Both were more common and more marked in the cases with aortic arch syndrome than in those without and it is possible that all 14 patients had had such symptoms despite the absence of such notes in their records.

In many of the cases with aortic arch syndrome the E. S. R. was markedly raised (Fig. 27). The mean maximal E. S. R. in 11 of these cases in series A was 120.5 ±SD 21.4 mm, compared with 101.7 ±SD 27.2 mm in the other cases in that series. This difference was significant ($p < 0.05$). For all 14 cases with the aortic arch syndrome the mean maximal E. S. R. was 120.6 ±SD 0.9 mm and for the other 79 cases in the entire material 99.8 ±SD 20.9 mm. The difference was significant ($p < 0.01$).

Selective unilateral or bilateral subclavian arteriography was performed in 8 of the 14 cases with the aortic arch syndrome and further in 3 cases without signs of aortic arch syndrome, but with murmurs over the arm arteries. The arteriographic findings in one of the latter cases are shown in Chapter 7 (case 83). Examples of severe stenotic changes in the main arteries to the arms are given in the following 3 case histories of aortic arch syndrome in PMA. A normal angiogram of these arteries is given in Fig. 28 for comparison.

Case 1. K. K. (Fig. 29). — A male factory worker born in 1889.

Until the summer of 1960 the patient had always felt well but now had pain in the neck, back and shoulders. The E. S. R. was 35—45 mm/1 hr. His physician treated him with local injections and he felt better. In December 1961 the pain in the shoulder and neck recurred. His doctor diagnosed the condition as "periarthritis humeroscapularis. The E. S. R. was 60 mm/1 hr.

About 15th November 1962, severe pain occurred in the gluteal and thigh muscles, especially in the flexors. One week later he also had pain in the calves. Even "brushing" of the legs by his clothes was painful. He could hardly walk and remained in bed. The slightest movement caused pain, which disappeared during complete rest. The neck and shoulder muscles were tender. *Neither then nor later had he headache.* He was first admitted to another hospital where interest was focused on the fact that the "slightest movement of the hip joints caused severe pain though the patient did not appear to have arthrosis of the hips. The E. S. R. was 122 mm/1 hr.

On December 12 1962 the patient was referred to the department of medicine in Växjö because of suspected myeloma. He had by then been ill for 6 weeks and the myalgia had almost disappeared. He was thin. He was not mentally senile. His muscles had apparently shrunk and felt flabby. Only the calves were slightly tender to palpation. The mobility of the large joints was normal. Apart from a coarse tremor of the hands, which he had had for a long time, neurologic examination revealed nothing remarkable. The heart sounds and heart rhythm were normal. No murmurs over the heart. Electrocardiographic recordings showed no abnormalities. The temporal artery pulsated well on both sides.

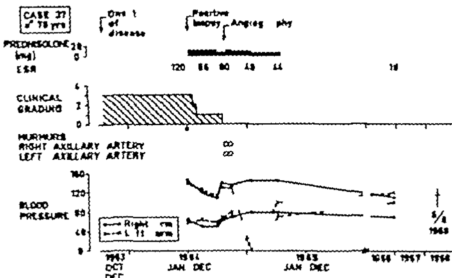


Fig. 3... Clinical course in case 37. For explanation of the diagram, see Fig. 29



Fig. 33. Arteriography of the left subclavian artery. Extensive irregularities of the arterial wall of the entire subclavian and axillary artery with marked luminal reduction in the most distal part of the latter and proximal part of the brachial artery. Only moderate collateral circulation. (Case 37)

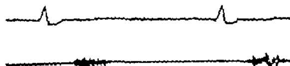


Fig. 34. Phonographic recording from left axillary artery 1 / years after onset of disease (case 37).

may trouble an elderly person so little that he might even not mention it to his doctor.

The clinical course and the angiogram of the arteries to the left upper limb are illustrated in Figs. 32 and 33 respectively. A phonogram of an arterial murmur in the patient is given in Fig. 34.

Case 82. E. S. (Fig. 35). — A farm labourer's wife, born in 1896.

The patient suddenly fell ill in Nov. 1967 with fever and after months' illness she was admitted to the department of internal medicine. During the first month of her stay there she had fever of unknown origin, but no local symptoms. Her body temperature was con-

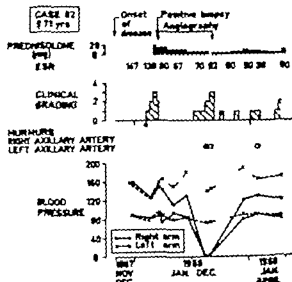


Fig. 35. Clinical course in case 82. For explanation of the diagram, see Fig. 29

timeously just above 38 C, she lost weight and became anaemic. Transient swallowing discomfort and tenderness to palpation along the neck muscles developed as well as marked dysgeusia and dysosmia, suggesting involvement of the carotids and cranial arteries. She had ny symptoms in the temporal region. A provisional diagnosis of PMA was made after the patient had been ill for 4 months, when initially fairly mild myalgic symptoms appeared as well as characteristic murmurs over the axillary and brachial arteries. For a short time she had bilateral pleural effusion.



Fig. 36. Selective arteriography of the left subclavian artery. Marked irregularities of the wall of the axillary and distal part of the subclavian arteries with marked narrowing of the lumen at the departure f the posterior humeral circumflex artery (Case 82).

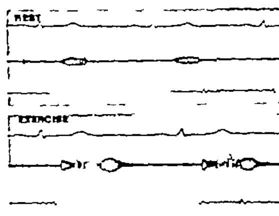


Fig 37 Phonographic registration of arterial murmur from right axilla before and after exercise (clenching the hand 20 times with arm elevated). Note appearance of diastolic component after exercise. (Case N 82).

The possibility of this being a sign of a collateral oedema of aortitis was considered. Signs of aortic arch syndrome appeared already in the 6th month of her disease (Fig. 35). Angiogram of arteries to left upper arm and phonograms from right axillary artery are given in F gs. 36 and 37 respectively

DISCUSSION

Historical

It is noteworthy that William Harvey (16.8) in the third chapter in *De motu cordis* seems to have described a case of aortic arch syndrome. Harvey had had the opportunity of examining a man with an aneurysm near in the transition between the right subclavian artery and the axillary artery The pulse in the same arm was fine, and the cause was explained at autopsy According to Harvey the major part of the blood flow was intercepted by the aneurysm and thereby interrupted the blood stream The patient s age was not given It is not possible to offer any acceptable explanation for the cause of the disease

One of the earliest cases of aortic arch syndrome on record was published by Savory*) (1856) under the title of "Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated The clinical picture and the post-mortem findings are described in detail.

The term aortic arch syndrome was used by Frövig (1946), who described the clinical picture of a 21 year-old woman from a Norwegian neurological clinic. Both radial arteries were pulseless, as were the neck arteries because of obliterating r teritis. In connection with this report Frövig published 4 similar cases. The first had been described by two of his compatriots, Raeder and Harbitz (1926).

Other cases had been reported by Marinesco and Kreindler (1936) and, from Japan, by Oota (1940) and Takahashi (1940). According to Frövig, thus 5 cases of bilateral obliteration of the common carotid artery had been diagnosed and published on the basis of non-syphilitic arteritis. All of the patients were women, aged 20—35 years. On the basis of these cases Frövig defined an aortic arch syndrome due to stenosis of arteries branching from the aortic arch. In addition to pulselessness

*) Like Harvey Savory was a tutor and demonstrator of anatomy and like Harvey he was also working at St. Bartholomew's hospital.

of these arteries the syndrome was characterised by neurological disorders resembling those seen in thrombosis of the internal carotid artery by ischaemic eye symptoms (cataract and iris atrophy), facial atrophy and a hypertension of other vascular territories.

Lindqvist (1948) has described the first two cases in Sweden of aortic arch syndrome on the basis of non-syphilitic arteritis. Ross and McKusick (1953) in a compilation of publications in European and American literature reported 10 possibly 13 cases of non-syphilitic, obliterating arteritis of the aortic arch and its large branches. Their series included the 5 reported by Frövig, but not the 2 reported by Lindqvist. Ross and McKusick contributed with 3 cases. They called them a "young female arteritis" variant of aortic arch syndrome They assigned some cases with considerable thrombocytosis to a separate group related to this variant Since thrombocytosis often occurs in association with giant-cell arteritis (Chapter 11) it is reasonable now to assign such cases to the group of non-syphilitic arteritis Ross and McKusick assigned to this group of non-specific, obliterating arteritis causing aortic arch syndrome also 33 cases reported from Japan (Shimizu & Sano 1951) Three of these cases were, however seen in men.

From a surgical clinic in Tokyo Shimizu and Sano (1951) reported 8 cases of non-specific arteritis, involving mainly the brachiocephalic arteries. The cardinal symptoms were pulselessness of the radial artery arteriovenous retinal shunts and later also cataract. The authors had found 25 similar cases in the Japanese literature and thought that the disease had not been reported outside Japan. These early Japanese cases had been reported by ophthalmologists under various symptomatic names or under the diagnosis of mb Buerger (Nasu 1963), mainly in Japanese language. In 1908 Takayasu reported a severe eye disease in a 21 year-old woman in Acta Soc. Ophth. Jap (cit. from Judge et al. 1962). She had remarkable, retinal, peripapillary wreath-like anastomoses between the arteries and veins and also developed cataract. Takayasu offered no explanation for the eye changes. In the subsequent discussion Oonishi and Kagoshima reported that they had seen similar cases, which were, however remarkable also in some other respects. In Oonishi s patient both radial arteries were pulseless, and in Kagoshima s, the left radial artery It has therefore been questioned whether it is justified to use Takayasu s disease as eponym for this idiopathic, obliterating arteritis of the brachiocephalic arteries. It is also claimed (Sano et al 1970) that it was Shimizu and Sano who in 1948 revealed that Takayasu s syndrome or arteriopathy is due to arteritis of the aortic arch and its main branches.

Nomenclature

Ross and McKusick (1953) used the term aortic arch syndrome to designate occlusive changes of the large arterial branches of the aortic arch with consequent symptoms of ischaemia in the areas supplied by such obstructed vessels, but unlike Frövig they widened the scope of the term to include such changes regardless of their etiology The term is generally used in this way today (Birke et al 1957 Judge et al 1962, Kappert 1964 Hunder et al 1967 Serre et al. 1968 Bernsmeier & Held 1970) In their comprehensive study Ross and McKusick analysed 100 cases of the aortic arch syndrome, including 35 previously unpublished cases. They recognised the following etiological groups: syphilitic aortitis, atheromatosis, trauma, congenital anomalies, chronic dissection of the aorta, thrombophilia, non-syphilitic arteritis, embolism and extravascular upper mediastinal tumour

The commonest cause in this material was syphilitic aortitis, especially the cicatricial type without aneurysm. In the discussion of the present material (after exclusion of the above thrombophilic group), only atherosclerotic and non-syphilitic arteritis are of interest as a cause of aortic arch syndrome Nowadays, syphilitic aortitis hardly ever occurs in the area covered by the hospitals in Växjö and Malmö

Takayasu s syndrome or arteritis (arteriopathy), pulseless disease, or young female arteritis are some of the many descriptive names (Judge et al 1962, Strachan 1966) most often used for an obliterating, cryptogenetic arteritis of the aorta and the large vessels of the aortic arch. As mentioned, the eponym has been criticised. This also applies to pulseless disease," but the term is expressive and says something clinically essential. The term "young female arteritis" was coined too early and since it limits the disease in respect of sex and age, it should perhaps be dropped.

Occurrence of pulseless disease

It is generally claimed that aortic arch syndrome on the basis of non-specific arteritis is more common in Japan than in Europe and U S A (Committee report 1968) and that the disease affects mainly women in fertile age (Bernsmeier & Held 1970). As for new uncommon or diseases difficult to diagnose, there appears to be reason to exercise caution concerning data about the frequency of a disease, its prevalence or predilection for certain ages or sex. There is a great risk that such figures may reflect differences in interest in the disease in question at different medical centres rather than give factual information

There is also a risk that obvious or unknown selection factors may influence the figures. It might be of interest to compare two roughly simultaneous sets of figures emanating from Japan and from the Western World.

Shimizu and Sano (1951) thus reported that 33 cases had been diagnosed in Japan, mainly on the basis of ocular symptoms. Ask-Upmark (1954) was able to trace 25 cases of "pulseless disease outside of Japan, to which he added 3 of his own Of these 28 cases, as many as 13 had been observed in the sparse population of Scandinavia (10 in Sweden and 3 in Norway) Two years later the number observed outside Japan had increased to 45 (Ask Upmark & Fajers 1956).

Extent of vessel changes in aortic arch syndrome

Without giving a precise definition of the term Ross and McKusick (1953) accepted obliterating changes as evidence of the aortic arch syndrome only if they were situated at "the origin of the great vessels from aortic arch and excluded those at a distance from the arch.

Most authors have probably used this diffuse definition Some investigators have, however accepted even a more peripheral localisation of the stenosis. Thus, on exposure of the carotid artery in several cases Shimizu and Sano (1951) found unusually firm adhesions all along the artery but these were most dense at bifurcations. Sano and Aiba (1966) reported that "thrombosis begins in very characteristic sites, namely in a portion of both subclavian arteries distal to the vertebral ramification and in the distal part of both common carotids just proximal to the bifurcation. Stenoses so peripherally as in the axillary and brachial arteries, and up to the base of the skull in the internal carotid artery have been observed at angiographic examination of patients with aortic arch syndrome (Wickbom 1957 Edling et al. 1961 Sandring & Welin 1961 Serre et al 1966 Sano et al 1970 and Bernsmeier & Held 1970) The observations in these publications are in good agreement with the author s definition of the aortic arch syndrome The papers, referred to above, on pulseless disease contain several illustrations showing obliterations and stenoses near the bifurcation of the carotid artery and in the axillary and brachial arteries. These arteries to the arms are usually not demonstrated in thoraco-cervical aortograms, which probably explains why the changes in the axillary and brachial arteries have not received the attention they deserve. In the patients angiographied in the present series of PMA with or without signs of aortic arch syndrome, the axillary and brachial arteries were studied at selective angiography of the subclavian artery In most of these cases the stenosis was most marked in the axillary artery often near the departure of the subscapular artery and the posterior humeral circumflex artery Judging from this material, the cicatricial process seems to spread in proximal direction along the vessel.

Variation of clinical picture age and sex distribution of the aortic arch syndrome with source of basic material

The clinical pictures, sex and age distribution of pulseless disease or of the aortic arch syndrome obviously vary appreciably with the character and composition of the primary material For example, Ross and McKusick (1953) based their description of the clinical picture of aortic arch syndrome on 40 of the 100 analysed cases. These 40 consisted of the best documented cases in which "there was involvement of at least two of the main brachio-cervical branches, of which at least one was a common carotid artery The clinical picture, thus depicted agreed largely with Frövig s syndrome, *i e* dominated by ischaemic cerebral and viscero-cranial lesions. Edling et al (1961) described the angiographic changes in Takayasu s arteritis in 14 cases, including 9 belonging to an earlier publication by Birke et al. (1957). In all 14 cases the vessels to the arms were changed, but only in 1 of the cases was stenosis of the internal ca-

rotid artery demonstrable. The difference in this frequency between the vessels was thought to be due to the fact that the roentgen department in question did not serve any neurologic clinic. There is also reason to assume that the selection was influenced by an over representation of patients with cardiovascular complaints in a very specialised cardiologic clinic, as in a material described by Schrire and Asherson (1964). The idea that the disease shows a strong predilection for women may explain why all 15 cases of pulseless disease on the basis of arteritis from an ordinary department of internal medicine (Sandring & Welin 1961) were women, while in the same publication 2 of 6 cases on a supposed atherosclerotic basis were men. Finally the present material of aortic arch syndrome in PMA was biased by the exclusion of patients with cerebral or cardial lesions.

Idiopathic/primary arteritis and aortitis syndrome

It has gradually become clearer and clearer that Takayasu's arteriopathy or pulseless disease should be regarded as a special manifestation of an idiopathic arteritis involving the aorta and large arteries to a varying degree and extent. Danaraj and Ong (1959) reported 2 children in Singapore with primary arteritis of the abdominal aorta, including the origins of the renal arteries, which caused stenosis and renal hypertension. Danaraj et al (1963) reported further 9 cases (a 30-year-old man and 8 women aged 15—32 years) with primary arteritis in different segments of the aorta and proximal parts of its branches. Hypertension with cardiac failure, encephalopathy and cerebral haemorrhage dominated the clinical picture in these cases, some of which also showed signs of the aortic arch syndrome. Similar observations have been made by Vinichaikul (1967) in a series from Bangkok consisting of 3 children and 5 women aged 21—48 years, and in Korea by Lee et al (1967) in a series of 10 children with pulseless disease. A large series of idiopathic arteritis with varying spread of vessel changes and with varying symptomatology has been reported from Capetown — from a clinical point of view by Schrire and Asherson (1964) and roentgenologically by Gotsman et al (1967).

The term aortitis syndrome has recently been used in Japan to mark the expanding clinical picture of primary arteritis. On the basis of clinical and pathological studies of 197 cases, including 72 examined at autopsy from a number of universities in Japan (Committee report 1968) the scope of the term aortitis syndrome included a variety of symptoms and signs due to inflammatory conditions of unknown nature in the aorta and its large branches. In the report is to be read. "When the lesions are confined to the aortic arch, the clinical picture corresponds to that of Takayasu's disease or pulseless disease. When the stenotic lesions are located in the descending aorta, the patient reveals symptoms and signs which simulate those of coarctation of aorta. Renovascular hypertension due to obstructive lesions of the renal artery is not infrequently encountered. Aortic regurgitation secondary to dilatation of the ascending aorta may be present. Occasionally aneurysmal dilatation is found in the areas other than the ascending aorta. In some cases the pulmonary artery may also be involved. Ueda et al. (1969) divided the changes of aortitis syndrome into 4 types according to their spread: aortic arch type, thoracic aorta type, abdominal aorta type and combined type. It is of interest to note that on the average, the patients' ages were higher in the cases of aortic arch type than in the others, suggesting that the localisation of the changes might vary with age.

Histology

There is no essential difference between the microscopic appearance of the arteries in idiopathic pulseless disease and that seen in giant-cell arteritis. The difference reported and considered important by some authors such as Nasu (1963) and Strachan (1966) — may perhaps be explained by differences in the intensity of inflammation or in the patients' ages. Because of the occasionally recurrent character of the disease one might also encounter "episodic" changes, *i.e.* both acute and chronic inflammation, simultaneously in a given case as well as reparative changes and pictures of healing sclerosis. Hamilton et al. (1971) felt that the microscopic morphology of Takayasu's disease is objectively indistinguishable from that of giant-cell arteritis.

Aortitis syndrome and giant-cell arteritis in PMA

Pathomorphologically it is apparently not possible to distinguish primary and idiopathic arteritis in Takayasu's disease or in aortitis syndrome from

giant-cell arteritis in PMA. In order to characterise the primary arteritis not only histologically but also clinically and anatomically Nasu (1963) suggested the name truncoarteritis productiva granulomatosa, and in view of the tendency of arteritis to sclerose and shrink the same Japanese pathologist suggested the term arterioscclero-cirrhosis. These descriptive names appear to be adequate also for giant-cell arteritis in PMA.

The difference in age and sex distribution between the two diseases is, however considerable. Most patients in Japanese series were 10—39 years old. Of 176 patients, 10 were at least 40 years of age (Committee report, 1968). In the earliest Japanese compilations male patients were rare. In the above mentioned committee report, however the ratio of men to women was 1 7 and in other compilations 1 6 (Nakao et al. 1967) and 1 4 (Ueda et al. 1969). The clinical relation between this primary arteritis, on one hand, and giant-cell arteritis and atherosclerosis, on the other has received little space in the Japanese literature.

In series of pulseless disease from the Western World there are relatively more elderly persons than in Japanese compilations. Of the cases published in U S. A. Barker and Edwards (1955) reported one of the first under the title "primary arteritis of the aortic arch. The patient was 64-year-old woman. In a compilation of 45 cases of Takayasu's syndrome outside of Japan (Ask Upmark & Fajers 1956), 13 patients were above 40 years and 6 above 50 years. Of 7 clinically firm cases of brachiocephalic obliterating arteritis, 3 were seen in patients aged 49 57 and 63 (Birke et al. 1957). Of 15 cases of pulseless disease on the basis of arteritis, 9 were above 40 years, 7 above 50 years (Sandring & Welin 1961). On the other hand, male cases of pulseless disease are at least equally uncommon as in Japan In 3 materials comprising together 32 cases (Ross & McKusick 1953 Sandring & Welin, 1961 Judge 1962) all the patients were women. In a survey of 45 cases there were 3 men (Ask-Upmark & Fajers 1956). In a series of 9 cases of pulseless disease on a probably arteritic base one of the patients was a man (Birke et al. 1957). Summing up, the ages of the Japanese patients were, on the average, lower than in series from other parts of the world, and the percentage of men was somewhat higher in Japan than in series from the Western World.

No satisfactory explanation can be offered for the difference in sex distribution between series from oriental and western series. The possibility that the forms of arteritis may be closely related, but not identical, must be considered. As pointed out above the lack of agreement may however, be due to irrelevant selection factors, and vague and arbitrary diagnostic criteria. The almost complete absence of elderly patients with pulseless disease in Japanese series is astonishing Western series of pulseless disease, on the other hand, often include elderly persons with signs of aortic arch syndrome on the basis of presumably non specific arteritis. Sandring and Welin (1961) could not find any reason for assuming that the disease affected young females only The authors stressed that the diagnosis of arteritis and its differentiation from cases with other causes of aortic arch syndrome are more difficult in elderly patients. This point is important in the discussion of the disease.

In the first publications of cases of aortic arch syndrome on the basis of idiopathic arteritis (Savory 1856, Raeder & Harbitz 1926, Frövig 1946) it was the severe neurological symptoms that dominated the picture. It is, however possible that these early cases were extremely severe and fatal variants clinically not representative of an arteritis, which generally does not take such a drastic course Ask Upmark (1954) pointed out that Takayasu's arteritis was anamnestically strikingly often of rheumatic character This was stressed by Sandring and Welin (1961) in their article Aortic Arch Syndrome with Special Reference to Rheumatoid Arthritis. Strachan et al. (1966) listed 67 cases of Takayasu's arteriopathy from western literature from the years 1948—1964 in which they had found reports on occurrence of diverse rheumatic symptoms, such as neck pain, stiffness of shoulders and back pain Of great interest are the clinical data in a recent Japanese publication (Nakao et al. 1967) In two thirds of these 54 cases there were systemic symptoms, such as malaise and moderate fever stiffness of the shoulders, nausea, anorexia, loss of weight and nocturnal sweating. Neither regarding laboratory findings in that material — anaemia, leucocytosis, raised E. S. R., electrophoretic changes and results of serological studies (Waaler Rose, latex fixation test and AST) — was there any fundamental deviation from the findings in corresponding examinations of PMA

Aortic arch syndrome and arteriosclerosis

Several publications (e g Gadrat & Moreau 195., Ross & McKusick 1953 Warren & Triedman 1957 Burstein et al 1957 Thurlbeck & Currens 1959) report cases of aortic arch syndrome classified as arteriosclerotic, though sometimes with doubt. The arguments for this are generally as follows 1) age above 50 years, 2) occurrence of diseases such as myocardial infarction, generally believed to be of arteriosclerotic origin, 3) normal E. S R The strength of these arguments may be questioned As is apparent from this publication, for example giant-cell arteritis is not uncommon in persons above 50 years. Sometimes the disease causes such considerable shrinkage of the large arteries as to give rise to aortic arch syndrome Giant-cell arteritis may cause myocardial infarction and claudication and, above all, atherosclerosis and co-existing arteritis are certainly common in these ages Afebrility and normal E. S. R. do not exclude an arteritic origin of the aortic arch syndrome It is true that in the present material of aortic arch syndrome in PMA the E. S. R. was always markedly raised, but it afterwards decreased. After withdrawal of steroid therapy the persistent aortic arch syndrome was often associated with only a mildly increased or normal E. S R.

Angiographic differentiation between aortic arch syndrome of arteriosclerotic and arteritic origin is presumably also difficult. It is true that Wickbom (1957) felt that arteritic stenosis had a more characteristic appearance with regular tapering of the vessel and smooth vessel walls, particularly in juvenile cases. Edling et al (1961) stressed the difficulty in angiographically differentiating the vascular changes in arteritis from other vascular changes — particularly arteriosclerosis obliterans it is easier to establish the changes than to determine their nature

Predilection for left side

As reported in the preceding chapter murmurs were somewhat more common over the left axillary and brachial artery than over the right. In some of those cases wher the murmurs over these arteries were bilateral murmurs were also heard over the arteries in the left arm one or more months earlier in the disease than on the right side, but never vice ersa No explanation could be found for this difference A s m la predominance was found on the left side for the subclavian and carotid arteries, but the significance of this predominance must be evaluated with caution because of the difficulty in differentiating between conducted cardiac and autochtonic murmurs over the juxtacardial arteries (Chapter 9).

Also the 14 cases of aortic arch syndrome suggested that stenosis tended to be more common in the arm arteries on the left side This difference was surprising, especially since much suggested that it was not due to chance. An arbitrary selection of cases of aortic arch syndrome on a firm or probable arteritic basis and selected from the literature were studied for differences in blood pressure and pulse between the arms (Jennings 1938, Lindqvist 1948, Myers et al. 1956, Birke et al 1957 Burstein et al. 1957 Crevasse & Logue 1958, Birke & Ekelund 1959 Liljefors 1960, Sandring & Welin 1961 and Judge et al 1962). In 37 of the cases in those series data given permitted comparison between the sides: in 26 the left arm was worse and in 11 the right.

This difference need not mean that the inflammatory changes has a greater predilection for the arteries in the left arm than for those in the right. It might be due to anatomic and haemodynamic factors. In large series of normals the blood pressure in one arm has been found often to differ from that of the other and the pressure in the right arm was often higher than vice versa (Korns & Guthrie 1933 Rueger 1951). It has also been shown that this holds also for hypertonics (Amsterdam & Amsterdam 1943). The difference in pressure between the sides was also on the average, greater for those persons with the higher pressure in the right arm A haemodynamic explanation of the differences in blood pressure in normals has been offered by Southby (cit. Amsterdam & Amsterdam 1943) This explanation is based on the lack of symmetry between the origins of the brachiocervical arteries from the aortic arch.

According to old anatomic measurements, the caliber of the left subclavian artery is somewhat smaller than the right (Vierordt 1906). Since shrinkage of a vessel wall will have a relatively greater effect if lumen is small than if it is large, the normal difference between the width of the right and the left subclavian artery might perhaps explain the greater tendency to stenosis in the arm arteries on the left side.

It is also noteworthy that pulselessness in the left

arm has been found to be much more common in large series of aortic arch syndrome in Japan (Committee Report 1968 Ueda et al. 1969).

Summing up the following observations of interest were made at follow-up of 93 patients with PMA for up to 8 years.

Fourteen patients had an aortic arch syndrome Of these, 11 showed arteritis at biopsy or post mortem examination. Ten of the patients developed with certainty this aortic arch syndrome after the onset of polymyalgia.

In more than half of the patients with aortic arch syndrome the syndrome developed within two years of the onset of polymyalgia

In one case it appeared within seven months.

In most of the cases examined angiographically stenosis was most marked in the axillary artery and often near the origin of the subscapular artery and posterior humeral circumflex artery

In some cases the radial pulse returned (as did the pulse of the temporal artery which may therefore be regarded as *pulsus redivivus*).

Pulselessness or significantly lower blood pressure was more common in the left arm than in the right.

The recovery of the radial pulse may be explained by development of collaterals. The lumen in the stenosed section may however also have become wider (Wickbom 1957) The greater tendency to stenosis in the left arm may be explained on anatomic and haemodynamic grounds and need not mean that inflammation as such has a predilection for the left side.

As long as the aetiology of Takayasu's idiopathic arteritis (pulseless disease) and giant-cell arteritis in PMA is unknown and as long as no specific diagnostic reactions are available, the identity of these arteritic forms cannot be established or excluded. The two types of inflammatory vascular changes resemble one another not only in appearance and spread but also from a clinical point of view This similarity is exemplified in a series of temporal arteritis (Chapter 12) which includes 2 young patients with (idiopathic) arteritis without any clinical or histological evidence of involvement of the temporal arteries.

HAEMATOLOGICAL STUDIES

On the basis of experience gained in the first 2 years (1961—1962) of the present investigation samples for laboratory studies were obtained from all patients on one or more occasions in the course of their disease and on one occasion from each of the controls. Blood analysis included enzyme stu dies (see Chapter 8) and analyses described in this chapter (Table 37) The investigation also included electrophoretic examination of the serum, thymol *turbidity test, determination of the plasma fibrinogen,* and serologic tests. The protein chemical and serological examinations are dealt with later (Chapters 13 and 14) together with corresponding exa minations in a material of temporal arteritis, syste matically investigated at the department of internal medicine in Malmö during the years 1952—1962.

LABORATORY METHODS

The laboratory methods accounted for in this chapter were performed routinely at the central la boratory for clinical chemistry at Växjö hospital (Head. Dr K. Jacobsson). The methods and the normal values at the laboratory are given in Table 37

MATERIAL

The material consisted of 51 cases of PMA with microscopically verified arteritis (series A) and 42 cases of PMA without histologically verified arteritis (series B) In what follows only blood analyses performed before institution of steroid therapy have been included and if a given analysis had been per formed more than once, the result of the first exa mination was used. In a few cases no determination was made of the haemoglobin, red blood cell count or white blood cell count before the beginning of steroid therapy Also other analyses are missing in some cases. As a rule, the blood samples used for the analysis were obtained on the same day or within a few days. About 60 % of the values given refer to the first and barely 30 % to the second half year of the disease In the remaining cases the blood samples were obtained later but always dur ing an active phase of the disease This is illumi

Table 37 Methods used in this chapter

Analysis	Method	Unit	Normal value (mean ± 2 SD)	
B-hemoglobin	Oxihemoglobin, Davies and Sheard (1927)	g/100 ml	male female	13.3—16.7 11.9—15.3
B-red blood cells	Celloscope counter (Ljungberg Instr Co., Sweden)	$10^6/\mu l$	male female	4.2—5.3 3.7—4.8
B-hematocrit	Capillary blood with Adams' autocrit centrifuge	per cent	male female	39—49 35—45
Ery-MCV	—	μ^3	—	86—102
Ery MCHC	—	g/100 ml	—	32—36
S-Fe	Shade et al. (1954)	μg/100 ml	male female	75—175 65—155
S-TIBC	Levy and Vitacca (1961)	μg/100 ml		250—380
B white blood cells	B rker counting chamber	$10^3/\mu l$		3—9
B eosinophiles	Rud (1947)	/μl		150—300
B-thrombocytes	Kristensson method according to Nordenson (1954)	$10^3/\mu l$		130—400
S-creatinin	Jaffé (1886)	mg/100 ml	male female	0.6—1.2 0.4—1.0

nated by the fact that at the time of these blood studies, the E. S. R. was more than 50 mm/1 hr in 85 % of the cases and over 100 mm/1 hr in 35 %. The E. S. R. was more than 50 mm/1 hr in 84 % of the patients in series A and in 88 % of series B. This difference is not significant.

The control material consisted of the 71 patients who in 1966—1968 were called in for re-examination, mainly concerning the peripheral arteries (Chapter 3). These examinations were carried out at the out-patient department as part of a general health control. Many of the controls had a long way to the hospital and many were also very old. None was confined to bed or wheel chair. As to their state of health, these controls may perhaps be regarded as representative of a non-hospitalised population in these ages, except in one respect: they had no rheumatic symptoms in their history and revealed no clinical rheumatic signs at the time of the re-examination. Of these controls, blood samples were obtained from 30 men and 35 women. In 2 of the women the E. S. R. was more than 50 mm/1 hr and knowledge of the E. S. R. in one man is missing. In the remaining controls the E. S. R. was less than 50 mm/1 hr and the mean and SD for the 29 male controls was 14 ±9.7 mm and for the 33 females 17 ±11.9 mm.

The normal range at the laboratory (Table 37) is valid for the selection period 1961—1968. These normal values are based mainly on younger individuals. A numerical comparison between the results of the analysis in the elderly patients and the normal values at the laboratory would therefore be of limited value.

RESULTS

Analyses related to anaemia. — Means for haemoglobin concentration, number of red blood cells, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), serum iron concentration and total iron binding capacity (TIBC) are given for the patients and for the controls in Table 38 (males) and in

Analysis	Group		Mean	SD	Difference between means for	P
B-hemoglobin	Series A	24	11.7	1.56	A—C 2.6	<0.001
	Series B	12	12.7	0.70	B—C 1.6	<0.01
	Controls (C)	30	14.3	1.68	A—B 1.0	<0.05
B-red blood cells	Series A	21	3.9	0.33	A—C 0.7	<0.001
	Series B	11	4.2	0.28	B—C 0.4	<0.05
	Controls (C)	30	4.6	0.50	A—B 0.3	<0.05
B-hematocrit	Series A	10	37.1	4.63	A—C 7.4	<0.001
	Series B	9	39.4	3.68	B—C 5.1	<0.01
	Controls (C)	29	44.5	4.67	A—B 2.3	>0.05
Ery-MCV	Series A	14	91.4	7.02	A—C 5.4	<0.01
	Series B	9	91.7	5.83	B—C 5.1	<0.05
	Controls (C)	30	96.8	5.30	A—B 0.3	>0.05
Ery-MCHC	Series A	14	31.7	1.62	A—C 0.6	>0.05
	Series B	9	32.9	1.51	B—C 0.6	>0.05
	Controls (C)	30	32.3	1.80	A—B 1.2	>0.05
S-Fe	Series A	18	38	23.9	A—C 71	<0.001
	Series B	10	56	24.5	B—C 53	<0.01
	Controls (C)	28	109	47.9	A—B 18	>0.05
S-TIBC	Series A	17	238	57.4	A—C 68	<0.001
	Series B	10	225	35.1	B—C 81	<0.001
	Controls (C)	28	306	64.4	A—B 13	>0.05

Table 38. Haematologic data on males with PMA and on male controls and comparison of the means found at these examinations between series A and B, on one hand, and controls, on the other, and between series A and B. See Table 37 for explanation of units.

Table 39 (females). It is clear from the tables that anaemia occurred in both sexes and that it seemed to be more severe in series A than in series B On comparison with the control material this anaemia proved microcytic and mainly normochromic. On comparison with the normal values at the laboratory (Table 37) the anaemia, however appeared hypochromic. The serum iron and total iron binding capacity (TIBC) were lower in all of the groups of patients than in the controls The difference was larger for serum iron than for TIBC.

White blood cells — The number of white blood cells was significantly larger in the patients than in the controls (Table 40) The difference was larger in series A than in series B In the patients as well as in the controls the number of white blood cells was larger in males than in females The difference was significant ($p < 0.001$) in series A, but not in series B or in the controls. The highest count found among the men was 18,300 compared with 15,300 among the women Both cases belonged to series A

Eosinophilic leucocytes — Fig 38 gives the values for the number of eosinophilic leucocytes found at the first examination and before institution of steroid therapy in 76 patients (42 from series A and 34 from series B) and in 61 controls. One of the 62 controls had 1 000 eosinophils per μl and coexisting transitory pulmonary infiltration and other symptoms and signs suggesting poly angiitis nodosa. This person was excluded from the control material By using Wilcoxon's rank sum test the difference between series A and the controls as well as that between series B and the controls was found to be significant ($p < 0.001$). No significant difference was found between series A and series B

More than 400 eosinophilic leucocytes per μl were found at the first examination of 14 patients in series A, in 8 of series B and in none of the controls More than 300 per μl were found in 17 cases of series A, 12 of series B and in 1 control. In series A the number of eosinophils at the first exa

Table 39 Haematological data on females with PMA and female controls and comparison of the means found at these examinations between series A and B on one hand, and controls, on the other and between series A and B See Table 37 for explanation of units.

Analysis	Group	n	Mean	SD	Difference between means fo	P
B-hemoglobin	Series A	26	11 1	1 64	A—C 2.5	<0.001
	Series B	24	11.3	1.33	B—C ..3	<0.001
	Controls (C)	35	13 6	1.29	A—B 0.2	>0.05
B-red blood cells	Series A	25	3 8	0.44	A—C 0.5	<0.001
	Series B	23	3.9	0.39	B—C 0.4	<0.001
	Controls (C)	34	4.3	0 41	A—B 0 1	>0.05
B-hematocrit	Series A	14	33 1	5 43	A—C 8.5	<0 001
	Series B	19	35.8	4.81	B—C 5.8	<0.001
	Controls (C)	34	41 6	3.67	A—B 2.7	>0.05
Ery-MCV	Series A	20	90.3	7.96	A—C 5 7	<0.01
	Series B	22	90.9	4.89	B—C 5 1	<0.01
	Controls (C)	32	96.0	5.87	A—B 0 6	>0 05
Ery-MCHC	Series A	20	32.0	1.48	A—C 0.8	>0.05
	Series B	22	32.3	1.28	B—C 0.5	>0.05
	Controls (C)	32	32.8	1.39	A—B 0.3	>0 05
S-F	Series A	22	36	23 1	A—C 48	<0.001
	Series B	20	36	22.4	B—C 48	<0.001
	Controls (C)	34	84	30.5	A—B 0	>0.05
S-TIBC	Series A	21	243	65.2	A—C 69	<0 001
	Series B	20	245	59.8	B—C 67	<0.001
	Controls (C)	34	312	50.9	A—B 2	>0.05

Group			Mean 10^9 1	SD	Difference between means for	P
Men	Series A	24	10.7	2.36	A—C 4.2	<0 001
	Series B	14	8.7	3.34	B—C 2.2	<0 05
	Controls (C)	25	6.5	2.02	A—B 2.0	<0.05
Women	Series A	25	8 1	2 29	A—C 1.8	<0.01
	Series B	25	7 9	2.89	B—C 1.6	<0.05
	Controls (C)	35	6.3	1 78	A—B 0.2	>0.05

Table 40 White blood cell count in each sex in series A and B, respectively and in controls.

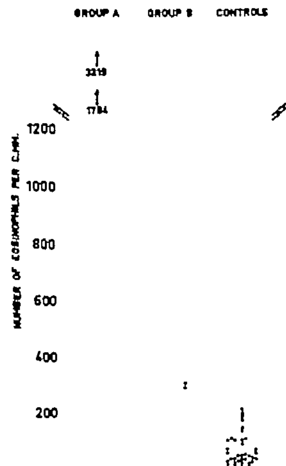


Fig. 38. Number of eosinophil leucocytes per μl in series A (42 cases), series B (34 cases) and control series (61 cases). The differences between group A and the controls like those between group B and controls are significant at the level of p <0.001 according to Wilcoxons rank sum test. (Group = series)

mination varied between 13 and 3.219 per μl, in series B between 13 and 936, and in the controls between 0 and 366

At the time of the highest individual eosinophilic count 33 of the 47 patients examined in series A were febrile (i. febrile and subfebrile) and 14 afebrile (Chapter 7) Of the febrile patients, 17 had more than and 16 less than, 300 per μl. The corresponding figures for the afebrile patients were 6 and 8 The febrile patients with eosinophilic counts of more than 300 were usually subfebrile, and in each case it was less than 38 C in the morning when blood was collected for the examination.

The highest eosinophil value of 3,219 per μl was found in series A, case 19 who developed an aortic arch syndrome. Of the 11 patients in series A with aortic arch syndrome (Chapter 10), however 6 had eosinophilic counts of at least 300 per μl and 5 lower than 300 per μl The corresponding figures for the patients in series A without signs of aortic arch syndrome were 19 and 17

Platelets — The mean number of platelets per μl in both groups was about 90,000 higher than in the control material (Table 41) The differences were significant (p <0.001). No significant difference was found with sex in either group The maximal value was 484,000 in series A, 476,000 in series B and 408,000 in the controls. When all the determinations in the patients be taken into account, the maximum value in series A was 543 000 and in series B 514,000

Group	n	Mean 10^9/ 1	SD	Difference between means for	P
Series A	40	301	89 1	A—C 91	<0.001
Series B	35	299	92.3	B—C 89	<0 001
Controls (C)	*64*	*210*	*54.9*	A—B 2	*>0.05*

Table 41 Platelet counts in series A and B and in controls.

Group	n	Mean	SD
Males			
Series A	21	0.8	0.12
Series B	10	1.0	0.43
Controls	25	1.1	0.23
Females			
Series A	20	0.8	0.18
Series B	21	0.9	0.22
Controls	35	0.8	0.23

Table 42. Creatinine in mg/100 ml in patients with PMA and controls

Creatinine. — The numerical data in Table 42 suggest that some of the controls had mild impairment of renal function. As expected, the mean value found for the male controls was somewhat higher than for the females, and the difference was significant at the level of $p < 0.001$. On the other hand, no significant difference was found with sex in either series of patients. On comparison between the male patients and male controls and between the female patients and female controls a significant difference ($p < 0.001$) was found only for the males in series A, in whom the mean serum creatinine was lower than that in the male controls.

COMMENTS AND CONCLUSIONS

When a person gets up from the lying position, a shift occurs in the body fluids from the intra- to the extravascular space, which means that the concentration of the blood cells and the plasma proteins is, on the average, higher in the standing than in the lying position. According to Jacobsson and Lindberg (1961), this has long been known. In the lying position the values for the blood cells and the proteins are, on the average, 8 % lower than in standing position (Laurell et al. 1970). Blood samples were obtained from the controls at the out-patient department, while the samples from the patients were obtained in the wards. This means that in some cases the samples were obtained while the patients were in bed. It is therefore possible that differences in posture during sampling may explain in part the calculated differences between the patients and the controls. In accordance with the routine at the department, most of the patients had been up for a while before collection of the blood samples. The differences found between the haematological values in the patients and the controls can therefore hardly be ascribed to any substantial extent to differences in posture during sampling.

Meulengracht drew attention to the systemic symptoms in shoulder periarthritis as early as 1945. As a typical feature of the serious cases he found normocytic anaemia with a normal colour index, which could not be explained by any coincident disease. Later authors have characterised the anaemia in polymyalgia as hypochromic (Bagratuni 1956, Barber 1957, Gordon 1960, Weissenbach et al. 1963, de Sèze et al. 1965). Olhagen (1963) described the anaemia in his material of polymyalgia rheumatica as hypochromic, sideropenic and refractory to oral iron therapy like anaemia in rheumatoid arthritis. In the present material of PMA the patients had microcytic anaemia with a lower hemoglobin concentration in series A than in series B. On comparison with the values found in the controls the saturation index was not significantly reduced. For the following reasons, however, it appears plausible that the anaemia in PMA may be hypochromic. Compared with the laboratory's normal values, the saturation index of the controls was slightly low and sometimes clearly subnormal values for MCHC were found. Further, in some single patients the anaemia was classified on more than one occasion before the beginning of steroid therapy and in those cases the MCHC showed a tendency to be falling.

The patients had considerable hypoferraemia and abnormally low TIBC. As in various chronic diseases (Wintrobe 1967), the basal features of anaemia in PMA are thus non-specific. The anaemia in rheumatoid arthritis was recently studied from various angles by Strandberg (1966). In the few respects in which a comparison with his work is possible, the anaemia in PMA does not appear to differ in type from that in rheumatoid arthritis.

In previous investigations of polymyalgia the number of white blood cells has been found to be normal (Holst & Johansen 1945, Barber 1957, Gordon 1960 and Olhagen 1963). Meulengracht (1950) found no certain evidence of leucocytosis in his series, but stated that the white blood cells had not been regularly counted in his material. Serre and Simon (1963) observed some cases with leucocytosis among their patients. Mild leucocytosis has been demonstrated in a fair number of cases in other series (Bagratuni 1956, 1963, Weissenbach

et al. 1963 de Sèze et al. 1965) In the first 7 cases of temporal arteritis reported from the Mayo-clinic (Horton & Magath 1937) the number of white blood cells varied between 7,500 and 13 000

It is clear from the present investigation that PMA is associated with mild leucocytosis The female patients in series A had a significantly ($p < 0.001$) smaller number of white blood cells than the males. No explanation can be offered for this difference

At the first determination of the white blood cell count, none of the patients in series A had a count below 5 000 In series B 2 women had between 4 000 and 5 000 white blood cells per μl and one woman had 2,100 In the last mentioned subject the leucopenia could, however be explained by the use of phenylbutazone. Leucopenia thus argues against a diagnosis of PMA.

In biopsy specimens from the temporal artery Winblad (1946) observed an admixture of eosinophil leucocytes in the inflammatory infiltrate in the vessel walls in 2 of 3 cases of clinical temporal arteritis. No clear blood eosinophilia had been mentioned in cases of temporal arteritis reported before that time. Winblad therefore felt that temporal arteritis resembled periarteritis nodosa and stressed that blood eosinophilia was not a constant symptom of periarteritis nodosa. The literature on temporal arteritis includes case reports with blood eosinophilia, but this sign is not mentioned as a characteristic feature of temporal arteritis in any large series (Andersen 1947 Roux 1954 Palm 1958). Blood eosinophilia has also occasionally been observed in PMA (Holst & Johansen 1945 Forestier & Certonciny 1953 Bagratuni 1953 Gordon 1960). Weissenbach et al (1963) reported that 9 of their 51 cases had blood eosinophilia of more than 4 and one patient had 17 % eosinophilic leucocytes 7 of the 45 cases reported by de Sèze et al. (1965) had eosinophilia of between 5—11 In the present material eosinophilia was a common finding in PMA and eosinophilia, as in periarteritis nodosa, sometimes appeared during the febrile phase of the disease. If the development of an aortic arch syndrome is a manifestation of a wider spread or of a more severe course of the disease (Chapter 10), the tendency to eosinophilia does not indicate a more serious form of the disease The reservation must, however be made that the number of eosinophilic leucocytes was determined on only one or a few occasions in each case and at widely different times during a protracted course of the disease.

Olhagen (1963) drew attention to the occurrence of thrombocytosis in polymyalgia, an observation which has since been made also by other authors. In the present material thrombocytosis was verified Since arteritis in PMA can cause aortic arch syndrome, it is noteworthy that considerable thrombocytosis has been described in cases of aortic arch syndrome (Nygaard & Brown 1937 Aggeler et al. 1941 and Frövig 1946).

Summing up, it should be stressed that anaemia, leucocytosis, eosinophilia and thrombocytosis are common blood morphologic features of arteritis in PMA and periarteritis nodosa, two forms of arteritis which are evidently closely related in these respects.

The comparison of the creatinine values between patients and controls lent no support to the assumption of any notable functional renal impairment in PMA, at any rate not during the fairly early phase of the disease when the examinations were performed

CLINICAL ANALYSIS OF 46 PATIENTS WITH TEMPORAL ARTERITIS FROM MALMÖ 1952—1962

INTRODUCTION

All cases of histologically verified temporal arteritis diagnosed at the department of internal medicine, Malmö (Head Prof Jan Waldenström) in 1952—1962 were re-examined and analysed by the author 1967—1969 The cases of PMA in the Växjö material were diagnosed in 1961—1968 Since the Malmö material had thus been observed before, and the Växjö material after the question whether the polymyalgic syndrome was related to temporal arteritis had been taken up for discussion in the press (Editorial in Lancet 1961), it was thought of interest to compare these two materials *from different angles*

This chapter concerns clinical data about the Malmö material and a comparison of it with the Växjö material from a clinical point of view In the next 2 chapters the two materials will be compared regarding serum-electrophoretic and serologic findings.

In all, the two materials comprised 85 cases of histologically verified arteritis (Växjö series A = 51 patients and Malmö series = 34 patients), most of which had been followed up systematically for several years.

MATERIAL

Between 1952 and 1962 all together 46 cases of temporal arteritis were diagnosed at the department of internal medicine, Malmö Not all of the patients had symptoms from the temporal arteries In those cases where such symptoms were missing it was considered on clinical grounds that the disease was temporal arteritis or some closely related condition

In 12 (4 men and 8 women) of these 46 patients the arteritis had not been histologically verified. Three of them were below 50 years at onset of the disease Arterial biopsy had been performed in only one, a 55-year-old man, who had developed signs of aortic arch syndrome in the course of his disease, but the examination had revealed no evidence of arteritis. His history was well compatible with a diagnosis of PMA. Of these 12 patients, 5 had died before the time of a review in 1970 but only one had been autopsied and no necropsy specimens of the vessels had been saved.

In the remaining 34 of these 46 cases (15 men and 19 women) arteritis had been histologically confirmed, and only these 34 patients will be dealt with in the following chapters. As in the Växjö material, 32 patients were above 50 years. One man (No 108) and one woman (No 134) were below 50 years.

The receiving area of Malmö general hospital covers only the town of Malmö which in 1958 *had a population of ..21 700 inhabitants The hos*pital is the only one in the town for acute physical diseases. The population served by the department of internal medicine in Malmö is thus twice that catered for by the department of medicine in Växjö All the patients except 2 belonged to the receiving area of the hospital All the patients were Scandinavians.

The cases in the Malmö series have been given 3 figured numerals (101—134) in order of the time of diagnosis.

EXAMINATION OF THE PATIENTS

The hospital records of all patients were studied Information of interest was extracted and noted All information about the symptoms, which were systematically sought in the Växjö material, were recorded. These included *inter alia* rheumatic symptoms On the basis of the data obtained diagrams were made of the course of the disease in each patient in the same way as in the Växjö material, *i. e* onset, rheumatic symptoms, biopsy of arteries, E. S. R. and steroid therapy Attempts were made to grade the rheumatic symptoms according to the same principle as that used for the Växjö material (Chapter 3) But the recording and grading of the rheumatic symptoms in the Malmö series were less reliable than in the Växjö material because these symptoms had not been described in such detail or followed for such a long time as in the Växjö material. Despite similar difficulties regarding the symptoms in the temporal region, attempts

were made to grade these symptoms according to principles applied in the Växjö material (Chapter 5). At the time of analysis of the Malmö material 19 patients were still alive, and 17 of them were reviewed. In these cases the patients histories were supplemented as far as possible. The patients were examined physically in the same way as in the Växjö series. The auscultatory findings over the arteries and the heart were recorded in the same way as in the Växjö material (Chapter 9).

Histological sections of the arteries were re-examined by Dr G Östberg of the department of pathology Malmö (Head Prof. F Linell.)

PATHOLOGICAL AND CLINICAL CONSIDERATIONS

As mentioned, 19 patients were still living at the time of the after-examination in 1967—1969. Four of these, however died soon after the review. Of the 34 patients, 19 were dead in the beginning of 1970. In 22 cases the diagnosis had been confirmed histologically by biopsy in 5 cases by biopsy and at autopsy and in 7 cases only at post mortem (Fig 39). In the 27 cases with positive biopsies the specimen in No 131 consisted of the uterine artery and in the others, of the temporal artery. In one (No 109) of the negative biopsies the specimen consisted of a piece of the temporal artery and in the other case (No 134) a small fragment of the radial artery — attached to the tip of the catheter after catheterisation — showed no inflammatory changes. In 25 of the cases giant cells were found in the inflammatory tissue.

According to the hospital records, 30 of the cases had been diagnosed clinically as temporal arteritis. Of the remaining 4 the clinical diagnosis was Morbus Takayasu in 2, namely Nos 107 and 134. These 2 patients were women, aged 64 and 16 years, respectively at the time of the diagnosis. Case 131 was diagnosed as Arteritis generalisata on the basis of changes of the uterine artery and is briefly described below. Case 108 was classified as non syphilitic arteritis. This case and No 134 will be described in greater detail as possible examples of juvenile variants of giant-cell arteritis.

The maximum E. S. R. varied between 50 and 139 mm/1 hr (mean 105 mm/1 hr) (Table 14 Chapter 7). According to the criteria used in the Växjö series, 30 of the patients had fever (Table 25 Chapter 7).

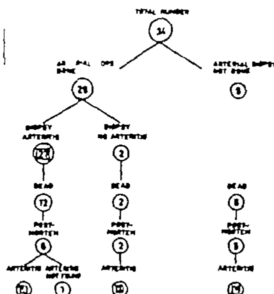


Fig. 39. Survey of clinical series of temporal arteritis diagnosed between 1952 and 1964 at the department of internal medicine in Malmö. All cases were histologically verified by biopsy and/or necropsy. (☐) denotes stage of histological diagnosis.

The records of 9 of the patients contained notes about the classical symptoms and signs of temporal arteritis, and in a further 13 such symptoms had been strongly suspected. Less characteristic symptoms of temporal arteritis had been noted in 6 cases, and in 6 the records contained no notes at all about head symptoms.

The records of all of the patients except 3 contained notes about rheumatic symptoms resembling those in PMA. In about half of the cases the descriptions of these symptoms were such that they satisfied the criteria for myalgic symptoms in PMA.

Judging from the descriptions, 4 patients had shoulder-hand syndrome, which had also been considered in a couple of them. Two of these patients were men (Nos 101 and 118) and 2 were women (Nos 112 and 125). The symptoms were bilateral in all 4.

According to the definition given in the description of the Växjö material (Chapter 10), 5 patients had the aortic arch syndrome. Four of them were women and 1 was a man. At last examination the blood pressure was not measurable by auscultation in the right arm in 1 and in the left arm in 1. The blood pressure was significantly lower in the left

arm in 2, and in the right arm in 1 compared with that in the contralateral arm A significant difference in blood pressure between the arms in the course of the disease had been noted in 1 case (No 119).

Diplopia had been noted in 3 cases and amaurosis or severe impairment of vision in 6 One patient was blind on both sides on admission to hospital. One became blind on the right side and 2 on the left side Impaired vision of the left side developed in 2 of the cases. Neither of these patients had been receiving steroid therapy at the time of involvement of the eyes. Patient 105 had been blind on the right side for 17 days and on the left side for less than 1 day before treatment with phenylbutazone. After 2 weeks the preparation was replaced by steroid therapy The patient became blind on both sides. Patient 106 became amaurotic on the left side during treatment with phenylbutazone Somewhat more than one day after the onset of blindness the drug had been replaced by ACTH and cortisone, but vision did not return In No 121 vision fell from 1.0 to 0 1 on the left side during treatment with phenylbutazone During massive steroid therapy vision improved from 0 1 to 0 4

Dizziness had been noted in 11 (32 %) of the patients and was often described as very troublesome. It generally occurred fairly acutely and persisted for weeks and months, but tended to regress The dizziness resembled that in central cerebrovascular disease

Systemic symptoms such as fatigue, loss of appetite and loss of body weight was more or less the rule Bodyweight had been noted on more than one occasion in 24 cases and in 15 of these the patients had lost more than 6 kg and 3 more than 14 kg.

As in the literature on temporal arteritis or giant cell arteritis (Hamilton et al. 1971) and in the Växjö material the hospital records of cases from 1952—196_ in the Malmö series contained data about the symptoms and signs which are now regarded as suggestive of this form of arteritis. They consist of manifestations from regions supplied by arteries involved. A list of such frequently transient and readily missed symptoms and signs that were noted in the Malmö series is given below

Necrotic lesions in the crown were observed in 2 cases (Nos 115 and 120)

Swallowing discomfort probably due to inflammation of the carotid arteries, was noted in 3 cases (Nos 110 113 and 126)

Buzzing, synchronous with the pulse in the head, was noted in 2 cases (Nos 121 and 125). After 2 years of the disease in case 125 a noise synchronous with the pulse occurred in the right half of the head, and at after-examination 7 years later (1968) it still troubled the patient. A strong murmur was auscultated over the right carotid artery just below the mandibular angle. It was audible up towards the right temple.

Masticatory claudication was described in 3 cases (Nos 111 123 and 126).

Patient 126 was troubled by swelling of the tongue and No 128 had lingua glabra

Tenderness over the vessels in the right upper arm was noted in case 117

Symptoms, like those in Raynaud's disease, in the arms were reported in 7 cases (Nos 104 107 114 120 122, 125 and 134)

Claudicatio intermittens in the legs was very painful in case 119 which responded favourably to ACTH-treatment.

One (No 102) of the earliest cases had in 1954 classical clinical temporal arteritis, which was verified histologically Biopsy of the deltoid muscle showed no changes in the interstitial tissue The blood pressure was 150/100 Half a year later the patient became worse and complained of migrating myalgia. At the same time haematuria appeared. The creatinine clearance was reduced. The arteritic process was thought to be confined mainly to the kidneys. During the following years the patient developed hypertension, and the blood pressure rose to 240/140 This hypertension was thought to have developed on the basis of arteritis (Associate Prof S. E. Björkman) The patient committed suicide in 1959 Legal post mortem did not include examination of arteries.

Apart from the eye-symptoms described above, neurologic symptoms were rare. In case 101 the knee jerk and ankle-jerk reflexes could not be elicited. The C. S F was normal, Wassermann's reaction was negative in the blood and C. S. F Lumbar puncture was performed in a further case soon after the development of diplopia and amaurosis (No 133). The C S F -protein was slightly increased (64 mg/100 ml) but there was no pleocytosis. In 5 cases (104 113 119 128 and 131) the patients had reported disturbances of the sense of taste and possibly also of smell during the disease

Diagnostic difficulties

In some cases in which the diagnosis had offered difficulties the patients had apparently been un necessarily operated upon In one case (No 119) a molar had been extracted before the patient had been referred to hospital. The severe headache did not improve and the patient wanted to have more teeth extracted, but her dentist refused. In the fol lowing 3 cases temporal arteritis had been suspect ed on admission of the patients to hospital but could not be histologically confirmed

Case 109 F A — This case, seen in 60-year-old woman, has been mentioned previously (Waldenström 1959). Themporal arteritis was suspected clinically in 1958, but at surgical exploration half year after on-set of the symptoms the operator could not find the temporal artery High E. S. R. and unexplainable fever indicated intravenous urography which showed an expanding process in the left kidney At surgical ex posure f the kidney the process was found to con-sist of renal cyst. The patient died 5 hours after the operation. Autopsy revealed a florid inflammation of the aorta and large arteries and of the coronaries. A fresh myocardial infarction was seen laterally in the left ventricular wall.

Case 116. E. J — This patient was a 63-year-old woman. The symptoms appeared in August 1960, and the following year the patient was admitted on 3 oc casions to the department of medicine because of Rheumatismus non definitus. Two months after onset biopsy specimen was obtained from the temporal artery despite the absence of local symptoms. The 1 cm long specimen showed no signs of inflammation. During investigation of the case the bromsulphalein retention was found to be 26 % after 30 minutes and the serum alkaline phosphatase was slightly increased (11 U Buch & Buch). The patient was not jaundiced. The patient was subjected to cholecystectomy The gall-bladder contained cholesterol stone but was not the site of inflammation. Biopsy of the liver revealed no-thing remarkable. A long time after the operation it was noted in the patient's records that the abdominal symptoms were correlated with the rheumatic pain. Tw years after the onset f the disease re-biopsy of the temporal artery showed giant-cell arteritis.

Case 131 A L—L — The patient was 59-year-old woman who had had pain in the muscles of the limbs for half year She was admitted to the department f internal medicine. E. S. R. was 127 mm/1 hr Pla telets 654,000 μl. She had not had headache and the essels in the scalp felt normal. Nevertheless tempo-ral arteritis was strongly suspected. However uterine carcinoma was suspected cytologically In June 1962 the uterus was amputated. No signs of carcinoma could be found in the operative specimen, but changes of giant-cell arteritis were observed in the uterine artery At operation a mass was felt at the top of the gallbladder for which reason she was subjected to cholecystectomy 1 month later A gallstone and slight *chronic cholecystitis was found. At later attempted* biopsy of the temporal artery the essel could not be found.

JUVENILE CASES OF GIANT-CELL ARTERITIS?

As mentioned, 2 of the patients were below 50 years. Since the disease in these 2 differed in some respects from the other cases, they are described below The first of the cases has been briefly re-ported earlier by Waldenström (1959)

Case 108 T S — The patient was salesman, who died in 1960 at the ge of 42. He was not living in the receiving area of the hospital and had been treated mainly at the department of internal medicine in Lin-koping by Dr Frey Lundmark. This colleague and Prof S. Larsson, Dept. of ophthalmology Lund re ferred the patient to Prof. Waldenström for investi-gation.

The patient was operated upon in 1950 because of assumed tuberculous epididymitis. In 1951 periphle bitis retinae (Eale's disease) was diagnosed, with changes mainly in the left eye. The aetiology of this disease of the eyes is unknown, but tuberculosis has been regarded as probable cause by some authors. It is known that since 1953 the patient had continuous-ly had raised E. S. R. which was usually between 75—100 mm/1 hr in 1955—1957 In 1957 steroid therapy was started and continued, usually in dose equivalent to 50 mg cortisone until the patient's death. In January 1955 fairly severe *pain occurred in the shoulders and neck*, sometimes with impairment of range f movement. After half year the pain re-gressed, but he still had muscle pain when the weather was bad. At the end of 1955 he was admitted to the department of internal medicine in Linköping. The E S R. was then 80 mm/1 hr. Total eosinophils 388/μl. Mantoux (3 mg) was negative. Chest x-ray revealed nothing remarkable and the heart was both roentgeno-graphically and physically normal. Sarcoidosis was suspected but not histologically confirmed.

Waldenström saw the patient for the first time in April 1956. The E. S. R. was 75 mm/hr Electropho-resis showed albumin 5.00, α_1-globulin 0 47 α_2-globu-lin 1 04 β_1-globulin 0.80, β_2-globulin 0.37 γ-globulin 1.23 g per 100 ml serum. Interpretation: "The pattern is compatible with any chronic inflammation. Re-

markably high albumin value. In view of the negative tuberculin reaction the histological sections of the epididymis from 1950 were re-examined by Associate Prof. N O Berg, Lund, who reported "Chronic, non-specific epididymitis with spermatogranuloma. In January 1957 the patient was admitted to the department of internal medicine, Malmö for observation. He was in a good general condition. He was afebrile. E. S. R. 60 mm/1 hr The electrophoretic pattern was largely the same as that found in April 1956. W R. in the blood negative. Total eosinophils 350 and platelets 298,000 per μl. Physical examination of the heart revealed nothing abnormal. Blood pressure right arm 130/85 left arm 125/95 Chest x-ray showed a normal-sized heart and normal lung fields. The aortic arch was dilated, which was very clearly seen in the tomogram. Re-examination of earlier roentgenograms since 1952 showed a successive dilatation of the aortic arch, which had originally been of normal appearance. The condition closely resembled Takayasu' disease, and the case was classified as non-syphilitic aortitis. Steroid therapy was recommended.

In September 1958 Waldenström saw the patient again. The patient had on both sides of the neck swelling, which had been interpreted as goitre. It was, however found that the swelling was due to marked dilatation of the carotid arteries. The swelling appeared to decrease both proximally and distally A systolic murmur was heard over the carotids and a frémissement was felt over the vessels. Both phenomena were most distinct under the right mandibular angle. The murmur had the character of a stenotic murmur Roentgenologically the heart had increased in size. Especially the aorta had dilated further and reached the anterior wall of the thoracic cage. At the level of the arch the aorta was at least 10 cm wide in diameter

In January 1960 the patient was again admitted to his local hospital because of incipient cardiac incompensation. Physical examination revealed considerable enlargement and an enhanced apical thrust in the sixth intercostal space. A presystolic and early diastolic murmur was heard over the apex of the heart and a sawing systodiastolic murmur over the base of the heart. The right radial artery was tense and pulsated strongly the left radial artery was barely palpable. Blood pressure right arm 140 60 left 120/90. Incompensation and cardiac dilatation progressed markedly and the patient died in June 1960 (As to post mortem see Appendix.)

Case 134 Ch. L. — The patient, a female student, died in 1964 at 17 years of age The clinical diagnosis was Morbus Takayasu. Post-mortem examination confirmed the diagnosis of arteritis (Appendix). It is not known when the vascular disease started After tonsillitis in 1957 she had rash over a large part f the body The rash persisted for one month and its true nature was never cleared up. The E. S. R., measured on 2 occasions, was 26 and 35 mm/1 hr respectively

During sinusitis in the spring of 1962 the E. S. R. was raised, and did not return to normal. In the autumn of 1962 *she had pain in the arms*, probably first in the forearms and later also in the upper arms. The pain did not disappear completely It was not accentuated by work. The arms felt numb. She often awoke at night because of pain and paresthesia of the arms and legs. Occasionally she was troubled by cramps in the calves. In the winter of 1962—1963 the E. S. R. varied between 31 and 52 mm/1 hr

In the autumn of 1962 she had nocturnal dyspnoea. In the autumn of 1963 the dyspnoea progressed. She was referred to the department of internal medicine in January 1964 because of suspected congenital or ganic heart disease and spent more than 2 months in hospital. On admission she was lean, she had lip cyanosis and resting dyspnoea. On exertion rales were heard over the lungs. Over the heart a regular rhythm was heard with a frequency of 130. A systolic murmur with a maximum over the second right intercostal space was heard. Blood pressure right arm 165/135 left arm 120 systolic. The left radial artery pulsated only faintly compared with the contralateral artery Systolic murmurs, probably autochtonic, were heard over the carotids. A frémissement was felt over the right carotid artery The blood pressure in the left arm was repeatedly lower than in the right, and was much higher in the legs than in the arms. In April 1964 the blood pressure was 175/135 in the right arm, 145/125 in the left arm, 235/135 in the right leg and 230/135 in the left leg. ECG showed sinus tachycardia and the pattern of left-sided prepoderance.

Chest x-ray showed moderate enlargement of particularly the left half of the heart and signs of congestion of the lungs.

Thoraco-cervical aortography showed complete occlusion of the left subclavian artery 1 cm from its departure from the aorta. The left vertebral artery was filled in retrograde direction and the left arm artery received blood also via collaterals from the descending aorta. Mural changes were also found in the right subclavian artery 7 cm from its departure from the brachiocephalic trunk.

For 5 weeks the patient was observed without steroid therapy She was afebrile, and the E. S. R. varied between 26 and 35 mm/1 hr Serum electrophoresis revealed moderate activity The gammaglobulin value was 0.94 g/100 ml. The electrophoretic changes were largely the same as in 1962. W R. in the blood was negative AST was negative. The examination for rheumatoid serum factor was negative. Hb 10.2 g/100 ml Red blood cells 3 6 millions and white blood cells

7,800 per μl. No eosinophilia. Repeated examination revealed no ANF or LE-cells.

During steroid therapy the patient felt somewhat better. She was sent home on 8th April 1964 with a prescription for 15 mg prednisolone per day. After 4 days she was re-admitted in agony with ventricular fibrillation. Attempted resuscitation was unsuccessful.

LABORATORY STUDIES

The mean values found for haemoglobin, red and white blood cells and platelets are given in Table 43. Only values found before steroid therapy are included, and when several values were available the first was used. For comparison, the table includes corresponding values in 51 cases of PMA with histologically verified arteritis (series A in Växjö material). These values have been extracted from various tables in Chapter 11. The limits of the normal ranges of the variables in question (Chapter 11) are practically the same as those at the laboratory in Malmö.

The total number of eosinophils before institution of steroid therapy was noted in 26 cases. It varied between 32 and 1600 per μl. More than 300 per μl was noted in 7 and less than 300 in 19 of the cases. In these calculations only the first value in each case was considered. Of all the values noted before institution of steroid therapy the highest was 1934 per μl.

Of other blood studies during the investigation of these cases, the serum GPT was above the normal value (mean ±2 SD) at the laboratory in 3 cases in which it varied between 33 and 120 U (Wróblewski). In these cases the alkaline phosphatase level varied between 11 and 32 U (Buch & Buch). In 3 cases bromsulphalein retention after 30 minutes was measured and was found to be increased in of them 26 and 18 %, respectively. In the former case there was also slight increase of serum-GPT and alkaline phosphatase.

ARTERIAL MURMURS

Of 17 patients examined, 9 (53) had arterial murmurs according to the definition given in Chapter 9. These 9 patients included 4 of the 5 with aortic arch syndrome. Murmurs were heard over 23 brachio-cervical vessels and 7 caudal (i.e. femoral and popliteal arteries). Murmurs were heard over all together 30 arteries in 9 patients, which means 3.3 per patient. In 8 (47 %) of the cases murmurs were heard over 2 or more arteries. Of the 17 patients, 6 (35 %) had murmurs over the arm arteries and in 5 of them the murmurs were bilateral.

CLINICAL COMPARISON BETWEEN MALMÖ MATERIAL AND VÄXJÖ SERIES A

Excluding the 2 patients who were below 50 years at onset and in whom the possibility of another type of arteritis cannot be excluded, the Malmö series consisted of 14 males and 18 females. The corresponding figures for the Växjö series A were 25 and 26. There was no significant difference in sex distribution between these materials. The mean age at onset was 70.1 in the Malmö series exclusive of the two patients below 50 years and 69.8 in the Växjö series A. The corresponding figures for the male patients alone were 71.9 and 70.6, for the females 68.7 and 69.1. There was no significant difference in age at onset between this Malmö material and the Växjö series A as a whole or for either sex.

The frequency of various symptoms in the two series is given in Table 44. No significant diffe

Table 43. Blood values in 34 histologically verified cases of temporal arteritis before steroid therapy at the department of internal medicine in Malmö 1952—1962. Values in brackets refer to 51 cases of PMA with histologically verified arteritis diagnosed at the department of internal medicine, Växjö, in 1961—1968 (Chapter 11).

Analysis	Sex	Unit		Mean	SD	Normal values (mean ±2 SD)
Hemoglobin	M	g/100 ml	15 (24)	12.4 (11.7)	1.48 (1.56)	13.2— 16.6
Red blood cells	M	10^6/μl	15 (21)	4.. (3.9)	0.52 (0.33)	4.0— 5.4
Hemoglobin	W	g/100 ml	19 (26)	11.3 (11.1)	1.63 (1.64)	11.6— 14.9
Red blood cells	W	10^6/μl	19 (25)	3.7 (3.8)	0.44 (0.44)	3.7— 4.8
White blood cells	M+W	10^3/μl	33 (49)	7.3 (9.4)	1.87 (2.32)	4 — 10
Thrombocytes	M+W	10^3/μl	13 (40)	422 (301)	283.3 (89.1)	150 —350

py This case is of interest in connection with the case (No 119) in the Malmö material in which the patient also had intermittent claudication of the legs. ACTH-treatment had an excellent effect on the ischaemic pain.

As in the Växjö material, also in the Malmö material there was one case with loss of knee jerk and ankle jerk reflexes.

Balmforth (1964) described a case of histologically diagnosed giant-cell arteritis in the temporal artery which developed the following changes occurred in the order given symptoms of polymyalgia, temporal arteritis, gangrene of the scalp, myocardial infarction and acute renal insufficiency The renal disease disappeared completely on institution of steroid therapy On the basis of a personal case Knorring et al. (1966) discussed renal involvement in temporal arteritis. Balmforth reported that he had not been able to trace such a case in the literature. It is therefore noteworthy that in this material there was one case (No 102) of temporal arteritis, diagnosed in 1954 with simultaneous signs of renal disease This patient also developed arterial hypertension later It is known from autopsy material that also the renal arteries can be involved by giant-cell arteritis.

It is noteworthy that, as in the Växjö material, some patients were operated upon on erroneous indications. Also in the Malmö material one patient was submitted to laparotomy twice without the discovery of any positive changes on either occasion. Such cases underline how important it is for the clinicians in the various specialities to recognise these cases and to include the diagnosis of PMA or temporal arteritis in their differential diagnostic considerations. The Malmö cases illustrate also how important it is for the surgeon to be well acquainted with the indication for biopsy and the value of really trying to find a representative piece of the vessel. It is therefore also useful to know before operation that it is the actual vessel involved that may be most difficult to find at exploration.

Of the 51 histologically verified cases of arteritis in the Växjö series A, eye symptoms occurred during steroid therapy in one (No 6). The patient became blind on both sides during treatment with triamcinolone The dose was small and inadequate. No such cases occurred in the Malmö series during steroid therapy and in one case vision improved after institution of steroid therapy as it did in one case in the Växjö series A.

During treatment with phenylbutazone (Björkman 1958) one of the patients in the Malmö series became blind on one side, and in a further case vision became severely impaired. In view of the risk of blindness it is surely unwise to use phenylbutazone and oxyphenbutazone instead of steroids in the treatment of patients with polymyalgia (Wadman & Werner 1967).

Half of the Malmö patients were reviewed 6—12 years after the active phase of the disease. Although this material is relatively small, it is noteworthy that characteristic stenotic murmurs were found such a long time after the onset of the disease and that the frequency and sites of these murmurs did not differ significantly from those in the Växjö series of PMA.

Regarding the two patients in the Malmö material below 50 years at onset of disease reference is made to the discussion of the possible relation between the cases of aortic arch syndrome in PMA and in the "aortitis syndrome in Chapter 10.

PROTEIN CHEMICAL STUDIES OF THE BLOOD

INTRODUCTION

The crusta phlogistica was rediscovered by Fåhraeus (1921), who described the phenomenon as a reduced stability of the suspension of the red blood cells. He devised a method for measuring the sedimentation rate of the erythrocytes (E. S. R.) and studied its dependence on the fibrinogen content. In most parts of the world the E. S. R. is now probably measured with Westergren's original simple method (1921). In the investigation of physical diseases the E. S. R. plays an important role in modern medicine.

Though not all of the factors contributing to an increase of the E. S. R. are properly understood, it may be regarded as established (Jeannet 1964) that the increase is generally due to quantitative, and probably also qualitative, changes of the plasma proteins. During the last few decades analyses based on the physical, chemical and immunological properties of the proteins have led to the elaboration of more refined methods for separating and characterising plasma proteins, advances which have proved invaluable to clinical research. Of special relevant importance was the advent of paper electrophoretic methods for separating serum proteins, which thanks to their simplicity are suitable for routine clinical work (Cremer & Tiselius 1950, Laurell et al. 1956). In the investigation of patients with a raised E. S. R. of obscure nature paper electrophoretic examination now plays a classifying role, corresponding to the determination of red cell constants in the investigation of anaemia. In patients with a raised E. S. R. there are thus 3 common findings which may provide valuable clues in the further investigation of diagnostically obscure cases. These findings are (1) increase of alpha-globulins, which is usually positively correlated with the fibrinogen concentration in the plasma, (2) monoclonal and (3) polyclonal hypergammaglobulinaemia (Waldenström 1968).

This chapter concerns paper electrophoretic examinations of serum in the Malmö-Växjö-series of patients with temporal arteritis and PMA, respectively. It also includes determinations of the fibrinogen in the plasma and the results of the thymol turbidity test in the Växjö series. The findings are compared with those made in corresponding investigations of elderly individuals selected according to certain principles (Chapter 2) from patients of Växjö hospital. This series will hereinafter be referred to as control material or control cases.

SERUM ELECTROPHORESIS FIBRINOGEN AND THYMOL TURBIDITY

Methods

The same method of paper electrophoresis was used in Malmö and Växjö (Laurell et al. 1956). The serum electrophoretic examinations, both in Malmö and Växjö were part of the routine service of the laboratories.

One and the same type of electrophoretic apparatus was used in Växjö and Malmö and the laboratory assistants at the Växjö laboratory had learned the electrophoretic technique at Professor Laurell's laboratory in Malmö.

The normal values for serum electrophoretic fractions were calculated on various occasions at the laboratories in Malmö (Table 45) and Växjö

	Healthy blood donors		
	1956 (n = 50)	1957 (n = 30)	1962 (n = 30)
	mean ± SD	mean ± SD	mean ± SD
Total protein	7.1	7.2	7.1
	0.26	0.28	0.35
Alb	4.5	4.6	4.8
	0.18	0.20	0.28
[illegible]	0.34	0.35	0.31
	0.04	0.04	0.04
	0.53	0.52	0.47
	0.05	0.06	0.06
β_1	0.50	0.50	0.51
	0.06	0.05	0.06
β_2	0.35	0.33	0.33
	0.05	0.05	0.05
	0.87	0.88	0.88
	0.11	0.12	0.11

Table 45. Distribution of serum proteins on paper electrophoretic fractionation according to Laurell et al. (1956). Mean values in grams per 100 ml serum. Registered blood donors in Malmö in 1956—1962.

(Table 46) The differences between the 3 series in Malmö were small and negligible The means were calculated for 2 representative normal series at Växjö laboratory viz. in the summer of 1965 (22 donors) and in the winter of 1968 (20 donors) The table also gives the means for the control material

The normal value for fibrinogen, at the Växjö laboratory determined according to Jacobsson s method (1955) was 0 18—0.36 (mean ±2 SD) grams per 100 ml plasma The normal value for thymol turbidity at the laboratory was 0 03—0 10 ext.units

	Healthy blood donors (n=42) mean ±SD	Elderly controls (n=62) mean ±SD
Total protein	7.2	7.4
	0.33	0.53
Alb.	4.9	4 7
	0.30	0.41
$_1$	0.24	0.27
	0 04	0.06
$_2$	0.40	0.54
	0.06	0.09
β_1	0 40	0.40
	0 06	0 08
β	0.30	0.36
	0 05	0.06
γ	0.91	1.09
	0 13	0.23

Table 46. Distribution of serum proteins on paper electrophoretic fractionation according to Laurell et al (1956). Mean values in grams per 100 ml serum. Registered blood donors and elderly controls in Växjö in 1965—1968

Material

In the following account of the serum electrophoretic examination of the Malmö and the Växjö series only the first examination in each case is considered (Table 48 and 47), and then only if it had been performed within the first two years of the disease and before institution of steroid therapy As for the Malmö patients, only those from 1955—1962 were included, because the routine method was not changed during that period A few cases in the Växjö series in which the exam n tion was performed before October 1961 are excluded, because before that time the normal laboratory value differed somewhat from that during subsequent years This difference may perhaps, have been due to a change in the quality of the paper used All Whatson s electrophoretic paper used at Växjö laboratory from October 1961 to 1968 was from a single batch

The results of serum electrophoretic examinations filling the above requirements are available for:

1 29 (85 /) of the 34 cases in the Malmö material Of these patients, 1 were males and 17 females.
2 4? (82 %) of the 51 cases in the A-series of the Växjö material Of these patients, 2 were males and 20 females
3 35 (83 %) of the 42 cases in the B-series of the Växjö material Of these patients, 1 were males and 23 females.

Of the 96 controls, serum electrophoresis was performed in 62 (65 %) Of these controls 30 were males and 32 females.

The total protein and the 6 electrophoretic fractions in the 3 above-mentioned patient groups and the control group were examined for any statistically significant difference with sex Such a difference was found ($p < 0\ 05$) only in series A and that was for γ-globulin, whose mean for men was 1 41 and for women 1.20 per 100 ml If the 4 groups and the 6 protein fractions be regarded as independent variables, a statistically significant difference will be found at the 5 % level only for 1 of the 24 variables. It was therefore considered warranted to pool the sexes in all of the materials

The investigation of the fibrinogen concentration in PMA was based on 6? (67 %) of the 93 cases in the Växjö material (Table 49). Of these, 37 belonged to series A and 25 to series B None of the patients had received steroid therapy before sampling In some cases the fibrinogen had been determined on more than one occasion before institution of steroid therapy and then the value obtained when the E. S R. was highest was selected for the analysis. In 56 cases the sample was obtained during the first year of the disease and in 6 during the second Of the 96 controls the fibrinogen was determined in 61 (64 %).

The thymol turbidity test in PMA was studied in 65 (70 /) of the 93 patients in the Växjö material None of these patients had received steroid

therapy before the time of sampling and the samples refer to the first two years of the disease. In a few patients examined on more than one occasion, the result obtained with the first sample was used. In 59 cases the sample was obtained during the first year of the disease and in 6 during the second. Of these, 37 belonged to series A and 28 to series B. The test was carried out on 60 of the controls.

Results

The values found for the total protein and electrophoretic fractions in series A and B of the Växjö material and in the controls are given in Table 47.

Table 48 gives the serum electrophoretic values for the cases of temporal arteritis in the Malmö material and, for comparison, values for a fictitious control material. This table is based on the assumption that the ratio between the normal values for registered blood donors in Malmö and values for a control material consisting of elderly persons, if such a series be selected in Malmö according to the same principles as in Växjö, should be the same as that between blood donors in Växjö and the control material there (Table 46). The relative difference between the two last-mentioned materials was calculated. The control material in Malmö was constructed by multiplying the normal values at the Malmö laboratory by this relative difference. In the calculation the normal values for 1962 at the Malmö laboratory were used.

It is clear from the electrophoretic values in the Växjö and Malmö materials (Tables 47 and 48) that both series contained signs of considerable activity reflected in the markedly increased values found for α_1 and α_2-globulin fractions and a marked reduction of the albumin fraction. A significant, though small, increase of the γ-globulin was found on comparison with the age- and sex-matched control material.

The mean fibrinogen concentration in the control material in Växjö was somewhat above the

Table 47. Electrophoretic distribution of the serum proteins before institution of steroid therapy in 77 of the 93 cases of PMA in the Växjö material. Series A = histologically verified arteritis, series B = not histologically verified cases. Controls and patients comparable in respect of age and sex distribution (see text).

Serum electrophoresis	Group	n	Means g 100 ml	SD	Difference between means for	P
Total protein	Series A	42	6.9?	0.512	A—C 0.44	<0.001
	Series B	35	6.93	0.427	B—C 0.43	<0.001
	Controls (C)	6?	7.36	0.528	A—B 0.01	0.05
Albumin	Series A	4?	3.32	0.524	A—C 1.38	<0.001
	Series B	35	3.51	0.480	B—C 1.19	<0.001
	Controls (C)	6?	4.70	0.412	A—B 0.19	>0.05
α_1-globulin	Series A	42	0.44	0.097	A—C 0.17	<0.001
	Series B	35	0.40	0.083	B—C 0.13	<0.001
	Controls (C)	62	0.27	0.063	A—B 0.04	<0.05
α -globulin	Series A	4?	0.97	0.222	A—C 0.43	<0.001
	Series B	35	0.87	0.205	B—C 0.33	<0.001
	Controls (C)	62	0.54	0.087	A—B 0.10	<0.05
β_1-globulin	Series A	4?	0.41	0.066	A—C 0.01	>0.05
	Series B	35	0.43	0.057	B—C 0.03	<0.05
	Controls (C)	62	0.40	0.075	A—B 0.0?	>0.05
β -globulin	Series A	42	0.47	0.113	A—C 0.11	<0.001
	Series B	35	0.46	0.114	B—C 0.10	<0.001
	Controls (C)	62	0.36	0.06?	A—B 0.01	>0.05
globulin	Series A	42	1.31	0.274	A—C 0.22	<0.001
	Series B	35	1.27	0.274	B—C 0.18	<0.01
	Controls (C)	6?	1.09	0.?33	A—B 0.04	>0.05

Serum electrophoresis	Group	n	Mean g/100 ml	SD	Difference between means for patients and controls	P
Total protein	Patients	29	7.3	0.64		
	Controls	30	7.3	0.56	0 00	>0.05
Albumin	Patients	29	3 66	0.48		
	Controls	30	4 60	0.38	0.94	<0 001
α_1-globulin	Patients	29	0.52	0 10		
	Controls	30	0.35	0 06	0.17	<0 001
α_2-globulin	Patients	29	1.00	0.17		
	Controls	30	0 63	0.09	0.37	<0 001
β_1-globulin	Patients	29	0.49	0 08		
	Controls	30	0.51	0.08	0.02	>0 05
β_2-globulin	Patients	29	0 43	0 10		
	Controls	30	0.40	0 06	0.03	>0 05
γ-globulin	Patients	29	1 19	0.32		
	Controls	30	1.05	0 19	0.14	<0.05

Table 48 Electrophoretic distribution f serum proteins before institution of steroid therapy in 29 of the 34 cases of temporal arteritis in the Malmö material. As for control material, see text.

upper normal limit (mean +2 SD) for healthy younger individuals Even compared with these elderly controls, who were not all healthy (Chapter 3), the fibrinogen values in the patients with polymyalgia were markedly increased (Table 49).

Group	n	Mean g/100 ml	SD	Difference between means for	P
Series A	37	0 72	0 181	A—C 0.33	<0.001
Series B	25	0 65	0 151	B—C 0.26	<0 001
Controls (C)	61	0.39	0 093	A—B 0.07	>0 05

Table 49 F brinogen values in series A and B and controls.

As for the thymol turbidity test, series A and B in the Växjö material were pooled (Fig 40) The values found in PMA were normal.

Comments

In series A of the Växjö material the mean values found for electrophoretic fractions, with the ex ception of β_1 fraction, deviated more from those in the controls than did those in series B (Table 47). Also the average value for fibrinogen differed from the control value somewhat more in series A than in series B (Table 49). Comparison of series A with series B revealed a significant difference ($p < 0.05$) only for the α-globulin fractions, while the differences for the other fractions and for fibrinogen (Table 49) were not statistically significant. These small differences between series A and B are probably due to the fact that the cases in series B

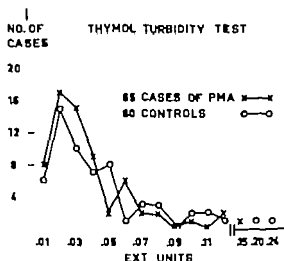


Fig. 40 Result of thymol turbidity test in 65 of the 93 cases of PMA (37 belonging to series A and 28 to series B) of the Växjö material and in a control material (see text).

were, on the average, less severe than in series A, both clinically and in respect of other laboratory values.

On the basis of Tables 47 and 48 the histologically verified cases of arteritis in the Växjö and Malmö materials are listed below according to deviations of the means of the total protein and electrophoretic serum fractions from corresponding means in their respective control materials:

	Växjö cases of PMA (g/100 ml) (n=42)	Malmö cases of temporal arteritis (g/100 ml) (=29)
Total protein	−0.44	−0.20
Albumin	−1.38	−0.94
α_1-globulin	+0.17	+0.17
α_2-globulin	+0.43	+0.37
β_1-globulin	+0.01	−0.02
β_2-globulin	+0.11	+0.03
γ-globulin	+0.22	+0.14

The agreement in the deviation of the α-globulins from the control value is striking.

As for the albumin fraction, it seems to deviate, on the average, more in the Växjö cases than in the Malmö cases, which can probably be explained by the fact that the electrophoretic examinations in the Växjö material were more often performed later in the course of a protracted disease than in the Malmö material (Fig. 41). This situation is also possibly reflected in the relatively somewhat higher mean value found for the γ-globulin in the Växjö material.

The β_2-fraction probably has the greatest methodological error (Belfrage 1963). The increase of the β_2-fraction in the Växjö series is, however significant at a level of $p < 0.001$. This increase could have connection with the rise in alkaline phosphatase, mentioned in Chapter 8 and might possibly indicate bile stasis.

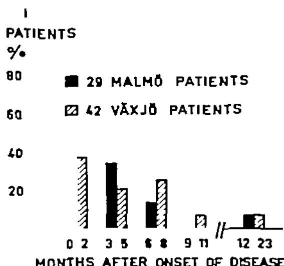


Fig. 41. Histologically verified cases of arteritis in Malmo and Växjo materials, distributed according to duration of the disease before the first electrophoretic xamination.

RELATIONSHIP BETWEEN E. S. R., FIBRINOGEN AND ELECTROPHORETIC SERUM FRACTIONS

In the Malmö material and series A of the Växjö material, *i. e.* histologically verified cases of arteritis, the E. S. R. and electrophoretic serum fractions were studied for any correlations. The fibrinogen content of the plasma was determined in the majority of cases only in the Växjö material. In that material also the E. S. R. and fibrinogen were studied for any correlation.

Material

The following analysis for correlations is based only on cases not treated with steroids before the time of sampling. Blood samples for measurement of the E. S. R. for serum electrophoresis and, in some cases, for determination of fibrinogen, were obtained on the same day or occasionally within a period of few days. The material was divided into 2 groups:

I. *Växjö material.* Of the 51 histologically verified cases of arteritis (series A) the E. S. R., and fibrinogen, and the serum electrophoretic pattern had been examined at roughly the same time in 33 patients (65 /). In some of these more than one of the fibrinogen determinations satisfied the above requirements. In such cases the first examination was selected if serum electrophoresis and measurement of the E. S. R. had been performed at the same time, otherwise a later value was used. In 27 of the cases the determinations were made in the first year of the disease, and in 6 in the second.

II. *Malmö material.* The comparison between the E. S. R. and electrophoretic fractions was based on 29 (85 /) of the 34 cases. The electrophoretic examinations are identical with those given in Table 48 and refer to the first 2 years of the disease. In

23 of the cases the samples were obtained during the first half year of the disease and in 2 during the second year

Results

Group I The correlation between, on the one hand, the variables fibrinogen, α_1 and α_2-globulin fractions and, on the other hand, E. S. R. was good in the 33 histologically verified cases of arteritis in the Växjö material (Fig 42) The correlation was roughly equally good but negative, between the albumin fraction and the E. S. R.

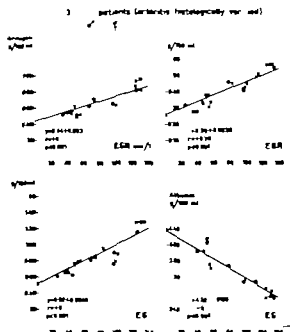


Fig. 42. Concentration of plasma fibrinogen, electrophoretic α_1 and α_2-globulin fractions and albumin in relation to E. S. R. in 33 cases of PMA with histologically verified arteritis.

In the same material the correlation between γ-globulin and E. S. R was not significant.

Group II For the 9 cases in the Malmö material the following values were found for the correlation between electrophoretic serum fractions (y) and E. S. R. (x)

Electrophoretic fractions		p
albumin	−0.55	<0.01
α_1-globulin	+0.46	<0.05
α_2-globulin	+0.39	<0.05
γ-globulin	+0.25	>0.05

DISCUSSION AND CONCLUSIONS

Methodological problems

As previously discussed (Chapter 11) differences found in haematological data between the patients and the controls could possibly be explained to some extent by differences between the materials in respect of posture of the body at sampling of the blood The concentration of plasma proteins is influenced by the posture in the same way as in the concentration of blood cells. Influence of posture, if any in the present investigation on the plasma proteins will have resulted in too small a difference in fibrinogen and the serum electrophoretic fractions (except albumin) and too large a difference for albumin. For reasons given in Chapter 11 however posture had at most a minor effect on the differences found.

The electrophoretic γ-globulin concentration has been reported to increase with age In a large control series (n=324 mean age 44.9 years) the regression coefficient was thus +0.03 g per 100 ml serum and 10 years classes (Leonardt 1964). In the author's personal control series (n=62, mean age 67 years) there is no significant correlation between age and γ-globulin concentration — the regression coefficient is −0.003 g per 100 ml serum per 10 years. This observation is of interest because this control material was not selected randomly but according to certain criteria (Chapter 2), which may have made the controls more comparable with the patients.

Earlier investigations

In Bagratuni's material of anarthritic rheumatoid disease (1956) there was an increased concentration of fibrinogen Hyperfibrinogenaemia in polymyalgic disease was found also by Serre et al (196.) and in a material of PMA with a high frequency of histologically verified arteritis (Alestig & Barr 1963 Hamrin et al. 1964 and Kogstad 1965) In serum-electrophoretic studies Bagratuni (1956) also demonstrated reduction of the albumin content and an increase of the γ-globulins. Similar electrophoretic changes have been reported in several series of PMA (Gordon 1960 Olhagen 1963 Alestig & Barr 1963 Hamrin et al 1964 de Sèze et al. 1965 and Kogstad 1965). Serre et al (1962) showed that the increase of the α_2-globulin was due to an elective increase of the haptoglobin In the present material the haptoglobin was determined only dur

ing the last 3 years of the collection period In these cases the increase of the haptoglobin was parallel to that of fibrinogen and of the E. S R

Electrophoretic examination as a diagnostic aid

The plasma protein pattern in acute infectious diseases and its variation during the course of the disease has been studied in detail by Belfrage (1963). He divided the functional, morphological and chemical changes associated with acute infectious diseases into two fundamental categories a) reaction to injury and b) reaction to foreign antigen. The former reaction occurs soon, within about a day and consists of fever leucocytosis and an increase of C reactive protein, increase of fibrinogen and electrophoretic α-globulins and reduction of the albumin fraction Reaction to foreign antigen causes, among other things, an increase of the γ-globulin. This occurs later in the course of the disease than the changes in the concentration of fibrinogen, α-globulins and albumin In acute infections the plasma protein changes reflecting the reaction to injury disappear within a few weeks, but those of the γ-globulin fraction much later The reactive changes to injury and the immunological changes are thus not synchronous.

In the present material of PMA and temporal arteritis samples were obtained for serum electrophoresis and determination of the fibrinogen usually only once or a few times before institution of steroid therapy Since these investigations were also performed during different phases of the disease, the material is not suitable for closer analysis of the chronology of the changes in the plasma protein pattern. However it is clear from the clinical description that the disease varies widely regarding character of onset, duration and tendency to exacerbation, which would also make such an analysis difficult Some patients did not receive steroid therapy at all, and some others only late in the course I a few of these cases the plasma protein pattern was studied repeatedly Observations made at such examinations suggest that the variation of the protein pattern during different phases of the disease resembles that seen in acute infectious disease (Belfrage 1963), except that the course in PMA is more protracted.

The term *active process* is often used for processes, including such phenomena as increased rate of cell necrosis, cellular defence reactions and reparatr e cell proliferation Active processes include not only acute infections, but also inflammatory conditions of other nature, thrombotic diseases, aseptic necrosis, collagen diseases and malignant tumours (Laurell 1966). Hyper-—globulinaemia occurs in some active processes and is marked in prolonged infections. An increase of the γ-globulin sometimes occurs also in the presence of malignant tumours, even though they are not secondarily infected, but the increase in —globulin is usually missing It is believed that a combination of high values for α_1 and α_2 globulin and normal γ-globulin argue for malignancy especially if the disease is protracted and associated with weight loss and the patient is afebrile or subfebrile. In PMA both the clinical picture and the electrophoretic pattern may mimic malignant disease. In PMA electrophoresis is, thus, of limited diagnostic value and provides hardly any guide in its differentiation from malignant tumour In order to exclude the type of renal cancer ushered in by a high E. S. R. and systemic symptoms but without urologic symptoms (Böttiger et al. 1966), roentgen examination of the kidneys is desirable even in cases with a clinical picture characteristic of PMA

From a biological point of view the electrophoretic serum fractions may be regarded as being polyvalent. The immunoelectrophoretic technique has permitted an increased specificity in the separation of serum proteins into far better defined components. There is reason t assume that the development of this and other techniques will result in new knowledge enabling more refined characterisation o the serum protein pattern in this form of arteritis.

Signs of activity

In active processes the increase in $_2$-globulin is largely due to an increase in haptoglobin, and the α_1-globulin increase to an increase in orosmucoid and $_1$-antitrypsin In acute infectious diseases haptoglobin and α_1-globulin are positi ely correlated with fibrinogen, like the haptoglobin with the α globulin (Nyman 1959). An increase in the haptoglobin by addition of purfied, concentrated haptoglobin preparation has no effect on the E. S R. (Jayle & Boussier 1955). It is generally accepted that the increase in the E. S. R in active processes is due largely to hyperfibrinogenaemia.

In the present PMA series a good correlation was found between fibrinogen and α-globulins, on one hand, and E. S. R. on the other. The E. S. R. in PMA thus gives a good idea of the concentration of the fibrinogen and α-globulins. Since the concentration of fibrinogen and α-globulins (like that of C reactive protein) is regarded as a good measure of the activity of the pathological process (Laurell 1966), it may be assumed that this also holds true for the E. S. R. in PMA. The greater the extent and severity of the tissue damage, the stronger these signs of activity. This is apparent from investigation of the effect of trauma of varying degree (Laurell 1966) and from the study of acute infectious diseases of varying severity (Belfrage 1963). The very strong signs of activity found in PMA may be ascribed to one or more of the following causes, which of course are not indepedent of each other: a) involvement of large vascular areas, b) ischaemic necrosis followed by repair of organs, perfused by the afflicted arteries, c) concomitant and widespread synovial and periarticular inflammatory process (Bruk 1967).

Polyclonal and monoclonal gammapathy

Polyarteritis nodosa, arteritis temporalis and the aortic arch syndrome due to arteritis are generally regarded as autoimmune diseases. But there seems to be some doubt as to whether these diseases are associated with a gammapathy (Waldenström 1961 and 1968). As is apparent from earlier analysis of polymyalgia arteritica, it appears warranted on clinical grounds to regard clinical temporal arteritis and aortic arch syndrome (due to arteritis) as rather uncommon manifestations of PMA. It is clear from the present material that hypergammaglobulinaemia is common in PMA. It should be noted that the increment is small (mean difference between patients and controls is as small as about 0.2 g per 100 ml). The Malmö and Växjö materials of histologically verified cases of arteritis contrast with Leonardi's series of systemic lupus erythematosus (1964) as does a later report on patients with SLE (Waldenström 1968), in which series 37 of 43 patients had definite hypergammaglobulinaemia (above 1.8 g/100 ml serum). Such high gammaglobulin values were found in 4 of the 29 cases of temporal arteritis in the Malmö material (highest value 2.05 g/100 ml) and in 7 of 51 cases (highest value 2.11 g/100 ml) in the Växjö material series A, i. e. all together in 11 of 80 verified cases of arteritis.

Electrophoretic separation of serum was done in all 34 cases with temporal arteritis in the Malmö material and in all 93 cases of PMA in the Växjö material. In one of the Malmö cases, mentioned by Waldenström (1968), a monoclonal γ-band was found with a concentration of less than 1 g/100 ml serum. In the A-series of the Växjö material (51 cases) no such band was found, while 2 cases in the B-series (42 cases) showed weak monoclonal bands. Of the 62 controls in the Växjö material, 1 showed a narrow band in the gammaglobulin region. M-components occur in roughly 3 % of all persons above 70 years (Hällén 1966). As both benign essential gammapathy (Waldenström 1968) and PMA increase in frequency with age, the present materials of temporal arteritis and PMA do not suggest that this form of arteritis should give rise to M-components. The possible relationship between monoclonal gammapathy and "pulseless disease" has recently been discussed following the report of one case of aortic arch syndrome in association with an M-component (Roberts et al. 1969).

Summary

The changes in the plasma proteins in PMA are characterised by unspecific signs of intense activity signs well correlated with the high E. S. R. The fibrinogen level is markedly raised, as are the electrophoretic α_1 and α_2-globulin values. A markedly low albumin concentration is a component of the electrophoretic pattern. In contrast with most autoimmune diseases, there is only a small increase of gammaglobulin fraction.

The present investigation did not lend support to the assumption that this form of arteritis causes benign monoclonal gammapathy.

CHAPTER 14

SEROLOGICAL INVESTIGATIONS

MATERIAL AND METHODS

Both in the series from the department of internal medicine in Malmö and in the series of PMA and control series from Växjö the following serological studies were performed according to the routine methods at the department of clinical bacteriology Malmö (Head. Professor S. Winblad):

Antistreptolysin 0 titration (AST)
Sensitized sheep cell agglutination test (SSC)
Acrylplast fixation test (Acryl fixation)

In the Malmö series the serological studies included also

Wassermann's reaction
Meinicke's reaction
Gonococcus complement fixation test
Bunnell's reaction

In the Växjö series the patients and controls were not studied for syphilis with Wassermann's test but only with Meinicke's reaction, which was performed at the central laboratory for clinical chemistry at the hospital (Head Dr K Jacobsson). The controls were serological examined on one occasion only

In the arteritis series from Malmö and in the series of PMA from Växjö serological reactions were performed usually on more than one occasion during the course of the disease. The frequency of the examinations in the Växjö series varied from 1 to 10 per patient and in the Malmö series from 1 to 6 The average frequency of the examinations for rheumatoid serum factor was about 3 per patient in the Växjö series and 2 in the Malmö series. Samples for serology were not obtained from the Växjö patients until after polymyalgia had been diagnosed on clinical grounds and the patients had been included in the material. The cases were thus not selected from patients with rheumatic symptoms and signs and with negative rheumatoid serum factor

In most of the cases in the Växjö series the first serological examination was performed after the patients had had the disease for more than 6 months. Many of the Växjö patients were followed serologically for several years. 82 of the Växjö-cases, *i e* all except 11 who had died, were examined serologically on at least one occasion in 1967—1968 (see Chapter 3) In 21 of the 34 cases in the Malmö series the last serological examinations were performed 1—13 years after the first examination. In barely half of the cases from Malmö and Växjö samples were obtained for determination of C reactive protein (CRP) These examinations were performed in various stages of the disease CRP was determined according to a standardised technique with reagents from the department of clinical bacteriology Malmö

RESULTS

Table 50 summarises the results of the serological tests. Only tests performed before steroid therapy had been started were included, and when the test had been performed on more than one occasion the result of the first test was chosen In the table the firm cases of arteritis in Växjö, *i. e* the 51 cases in series A, are pooled with the 34 cases of arteritis in Malmö, while the 42 PMA-cases not verified histologically from Växjö (series B) are treated separately It is clear that the frequency of positive serological reactions was low in all of the series. For the Waaler Rose test (SSC) the borderline value for the titer was set at 1/32 The only positive case among patients with arteritis had a titer of 1/64 and one of the controls had a titer of 1/64 and another 1/128

As for AST the frequency of positive titers (>210) was somewhat higher in series B than in the other 2 series. On comparison between series B and the controls in this respect no significant difference was found ($p > 0.05$) when cases with a borderline titer of AST were added to the negative group, while the difference would have been statistically significant ($p < 0.05$) if these cases had been assigned to the AST positive group The highest titer (850) was recorded in one of the controls.

If all of the some 300 serological examinations performed during and after the disease in 34 cases of arteritis from Malmö and in 93 cases of PMA from Växjö would be taken into consideration, it would not noticeably affect the distribution of posi

Serological reactions	Histologically verified arteritis			Controls			Cases of PMA—arteritis histologically not verified		
	(85 cases)			(71 cases)			(42 cases)		
	n	neg.	pos.	n	neg.	pos.	n	neg.	pos.
AST	67	58	5 (4)	61	54	7	34	23	8 (3)
SSC	70	68	1 (1)	64	62	2	35	34	0 (1)
Acryl fixation	62	57	5	50	43	5 (2)	33	33	0
WaR	34	34	0	—	—	—	—	—	—
Meinicke	81	80	1	65	65	0	35	35	0
GC-compl. fixation	26	26	0	—	—	—	—	—	—
Cold-agglutinin	26	25	0 (1)	—	—	—	—	—	—
Bunnell	26	26	0	—	—	—	—	—	—

Table 50. Results of serological studies performed before beginning of steroid therapy in 85 cases of histologically verified arteritis (34 cases from Malmö 1952—1962 and 51 of PMA, L Växjö series A from 1961—1968) and in 42 cases of PMA without histologically verified arteritis (Växjö series B). As for controls see text. Figures in brackets denote number of cases with borderline values.

tive and negative tests. The Waaler Rose test (SSC) was thus positive on some occasion in a further 3 of the cases of arteritis and in 1 of the cases in the B-series, and the acryl plast fixation test became positive in 4 cases of arteritis and a borderline value was observed in 2 cases in series B

Results of determination of CRP

CRP in mm	No of histologically verified cases	No. of cases in series B
0	3	2
1—	7	7
3—4	11	5
5—6	7	2
7—8	7	2
9—10	1	1
11—12	3	0
Total	39	19

CONCLUSIONS

Rheumatoid factor is uncommon in PMA. It occurred in low titer and not more often in PMA than in age and sex matched controls with no history or clinical evidence of rheumatic disease in the broad sense of the term The occurrence of rheumatoid serum factor in a case of rheumatism argues strongly against PMA

There is no reason to assume any serological relationship between *PMA* and syphilis, gonorrhoea or diseases with heterophilic antibodies or cold agglutinins.

PMA is not associated with any infection with haemolytic streptococci This postulation agrees well with the clinical observation that the onset of PMA does not appear to be related to infections of the respiratory tract more often than what can be ascribed to chance in epidemics of respiratory tract infections.

The occurrence of CRP in nearly all cases examined suggests that the disease is associated with tissue destruction (Hedlund 1961).

CHAPTER 15

GENERAL DISCUSSION

General Remarks — I feel that I have been scarcely able to prov my contention that these acute senile cases belong to a different category from gout and rheumatism on the one hand and rheumatoid arthritis on the other yet, if I have succeded in drawing the attention of medical men generally to a remarkable type of disease — emarkable in its severity and complete cura bilty even at a ery advanced time of lif — I shall, I hope be pardoned for dilating on the well worn subjects of gout and rheumatism.

(William Bruce British Medical Journal 1888)

POLYMYALGIA ARTERITICA AS A NEW DISEASE

The panorama of diseases varies both geographical ly and historically Definition of diseases is one of the important tasks of medical research. The best criteria of such definitions are of aetiological nature Classification of diseases of unknown or un certain aetiology offers difficulties. In such cases new clinical, pathological, biochemical and serological studies may reveal pathogenetic relations and thus necessitate revision f previous more or less well defined nomenclature.

In the last decade such observations have been made regarding the form of rheumatic disease which is known under different names and referred to in this paper as polymyalgia arteritica (PMA) It is characterised by above all, a raised E. S R periarticular pain and symptoms of "muscle rheu matism On the basis of clinical findings some authors assumed that temporal arteritis and its se rious ocular complication as well as the polymyal gic syndrome were clinical symptoms of one single disease generalised polyarteritis of the large arteries. This assumption gained increasing strength from the systematic examinations of the arteries in the present investigation and from other series of polymyalgia rheumatica A systematic review of cases of temporal arteritis seen at the department of internal medicine, M lmö in 1952—1962 lent f rther support to this assumption A was appa rent from the comparison between the Malmö series and the prospectiv investigation of the Växjö material (both series included only histologically verified cases) no statistically significant difference could be found concerning a number of variables, with the exception of local symptoms referable to the temporal region This difference evidently only reflects the difference in the importance attached to this symptom in the diagnosis of suspect arteritis. Since the patients in the Malmö series had not been systematically examined for rheumatic symptoms, the materials could not be compared regarding such symptoms. It was, however remarkable that in half of the cases in the Malmö material the records contained such good descriptions of rheumatic symptoms that they met the requirements of the criteria set up for the diagnosis in the Växjö ma terial. In only 3 of the patients in the Malmö series the records did not contain notes about rheumatic symptoms.

The number of histologically verified cases of arteritis seen at the department of internal medicine in Malmö in 1952—1962 was 34 *i. e* 3 per year During the period covered by the collection of the material in Växjö as many as 51 cases of histologically erified cases were diagnosed, *i* on the verage, 7 per year The department in Malmö caters for a population twice the size of that in the area served by the department in Växjö It is obvious that for the diagnosis of this form of arteritis, the rheumatic symptoms though not always easy to prove, are very important. As a matter of fact, such symptoms led the examiner's idea to the possibility of temporal arteritis in some of the later M lmö cases. Only 9 (25) of the patients in Malmö presented a classical picture of arteritis in the temporal region and 6 showed no such symptoms at all Though PMA may occasionally occur without more than transient rheumatic symptoms, it is obvious from the present investigation nd other publications that the rheumatic symptoms dominate the clinical picture, while other symptoms, particularly in the region of the tem poral arteries, are less common, and usually milder and shorter The conception of the polymyalgic syndrome (Meulengracht 1945 and 1950 Porsman

1951 Bagratuni 1951 and Barber 1957) has thus proved useful and means, among other things, that clinical temporal arteritis in its classical form with symptoms referable to the temporal region should now be regarded as an episodic and unusual clinical phenomenon in PMA (Hamrin 1966). A similar opinion was presented early by Scandinavian authors (Sjövall & Wimblad 1944, Andersen 1946). The rheumatic symptoms and signs in PMA are often diffuse, they are migratory and difficult to detect and prove. Sometimes they only last a few months or a year or two. They resemble what most people believe to be muscle rheumatism. It is possible that an arteritic process may be a more frequent cause of muscle rheumatism, at least the pain in the neck, shoulders and arms than spondylosis. Waldenström (1969) has pointed out that "muscle rheumatism," one of the classical rheumatic diseases so frequently encountered in clinical medicine but neglected by academic medicine, has again received proper recognition with the introduction of polymyalgia rheumatica.

PMA FROM A NOSOLOGICAL POINT OF VIEW

The relation of PMA to degenerative bone and joint diseases, collagen diseases and arterial diseases deserves attention.

As shown by the analysis of the rheumatic symptoms in PMA (Chapters 3 and 7), it is sometimes difficult to decide to what extent the symptoms should be ascribed to PMA or existing arthrosis. This is particularly so in patients with existing arthrosis of the knees and hips. As previously mentioned, the time interval between the onset of pain and the general symptoms may serve as a guide. Of greater fundamental interest is the distinction between PMA and degenerative changes of the vertebral column.

In the 1930s to the 1940s enormous strides were made in our knowledge of the pathogenesis and therapy of sciatica and some instances of brachialgia. Sciatica is often accompanied by backache and brachialgia by neck-shoulder pain. Symptoms of muscle rheumatism have therefore most often been ascribed to degenerative spondylotic changes even when no herniation of an intervertebral disc could be demonstrated. Hult (1954) classified muscle rheumatism into three syndromes: 1) symptoms from the neck and shoulders with or without radiation to the arms (stiff neck — brachialgia syndrome), 2) symptoms from the region of the dorsal spine with or without radiation along the ribs or out into the flanks (dorsal spine syndrome) and 3) low back trouble with or without radiation to the legs (lumbar insufficiency—lumbago—sciatica syndrome). The similarity between these spinal syndromes and painful symptoms in PMA is apparent already from this crude classification of muscle rheumatism.

The similarity will hardly be less in a more detailed study of these spinal syndromes. Thus, in Hult's material the frequency of "frozen shoulder" was given as 28 % of 162 cases. Common to both is also the relatively large variety of symptoms and the localisation and character of the pain in the neck, shoulders and arms. Both diseases are self limiting. In those cases where no herniation of a disc could be demonstrated it was difficult to relate muscle rheumatism to degenerative changes of the vertebral column. The indirect signs of disc degeneration on conventional roentgen examination of the spine are osteophytes on the margin of vertebral discs and narrowing of the intervertebral spaces. These spondylotic changes are progressive and will sooner or later affect all persons in advanced age. It is therefore difficult to correlate these changes with episodic and generally migratory symptoms of muscle rheumatism. The view that the above-mentioned syndromes are nevertheless due to degenerative changes of the spinal column is founded on the assumption that radial disc ruptures cause so to say incomplete herniation of discs or "ulcers" in the annulus fibrosus with inflammatory changes on the posterior part of the discs and involvement of nerve roots and pain-sensible tissue about the spinal canal. As with PMA, the frequency of spinal syndromes increases with age. It is obviously difficult to differentiate between these spinal syndromes on the basis of degenerative spinal changes without roentgenologically demonstrable disc herniation and PMA. Spondylosis *per se* is probably not an essential factor in the origin of the rheumatic symptoms. General symptoms in PMA may be readily missed, fatigue and depression may be regarded as a natural reaction to a painful condition, and it may be difficult to demonstrate loss of body weight by elderly persons, and in patients who have had the disease a long time body temperature and E.S.R. may be only slightly raised. Elderly per

sons often have several coexisting diseases and then a raised E. S. R. may be erroneously ascribed to a latent cholecystitis or urinary tract infection, for example. It should also be observed that in ischaemic conditions of the limbs paresthesia occur which may be readily misinterpreted as symptoms of irritation of a nervous trunk.

Concerning symptoms resembling those of muscle rheumatism, a correct diagnosis requires close observation of the patient not only regarding rheumatic symptoms but also for signs of systemic symptoms such as fever and E. S. R. as well as repeated examinations of the vessels.

Differentiation of PMA from rheumatoid arthritis has been discussed in Chapter 7 The ranking of rheumatoid arthritis by the American Rheumatism Association in 4 classes according to diagnostic certainty indicates that the disease is not easy to define. As pointed out in the discussion of the clinical picture of PMA, its clinical picture overlaps that of rheumatoid arthritis. There is thus reason to assume that published series of rheumatoid arthritis include cases of PMA PMA can be diagnosed with a high degree of probability on the basis of clinical symptoms, a characteristic course with involvement of arteries, no serological signs of rheumatism, and absence of roentgenological signs of arthritis. It is possible that a comparison between PMA with histologically verified arteritis, on one hand, and classical rheumatoid arthritis as codified by the American Rheumatism Association, on the other would improve the diagnosis of rheumatoid arthritis and reduce the degree of clinical overlapping Such a comparison should preferably be made on the basis of long-term studies of cases of classical rheumatoid arthritis and PMA, respectively with special reference to the onset of symptoms in the peripheral and proximal joints and the progressive or regressive nature of the disease.

Certain phenomena occur often or in a characteristic way in collagen diseases 1) polyclonal hypergammaglobulinaemia, 2) rheumatoid serum factor 3) cell specific antibodies and 4) tendency to simultaneous or consecutive appearance of two or more collagen or autoimmune clinical pictures. These problems have been dealt with in Waldenströms (1968) Flexner Lectures, which contain a detailed list of references. It is clear from these lectures and later publications (Waldenström 1969) that the clinical picture of angiitis differs from that of classical collagen diseases. This is also confirmed by the present investigation as far as hypergammaglobulinaemia is concerned, which is not a characteristic feature of PMA and the findings regarding negative rheumatic serology in PMA. Neither did any of the patients in the present PMA or temporal arteritis series show any distinct signs of other collagen or autoimmune diseases. In this connection it should be recalled that the investigation produced evidence that temporal arteritis and aortic arch syndrome on the basis of arteritis are clinical features of PMA. A few exceptions have been reported in the literature. Lessof & Glynn (1959) published a case of aortic arch syndrome in a 21 year-old woman with systemic lupus erythematosus and Serre et al (1966) a case of Takayasu s disease in a 58-year-old woman with a positive Waaler Rose reaction in a high titer One case of temporal arteritis with circulating anticoagulant, probably an antibody (Waldenström 1970), may be a further exception

As for the relation between PMA and other arterial diseases, polyarteritis nodosa, thromboangiitis obliterans (Mb Buerger) and arteriosclerosis deserve attention. Clinically in several respects PMA resembles polyarteritis nodosa, arthralgia, fever high E. S. R., thrombocytosis and eosinophilia (Talbott & Ferrandis 1956, Frohnert & Sheps 1967) Symptoms referable to visceral organs, however dominate the clinical picture and the prognosis is much gloomier in polyarteritis nodosa. It is quite plausible that this is because the vessels involved in polyarteritis nodosa are of smaller caliber than those affected in PMA In polyarteritis nodosa mainly the intravisceral small sized arteries (approximately below 1 mm) are involved In PMA, large and extravisceral. Steroid therapy is of significant value in polyarteritis nodosa (Frohnert & Sheps 1967) even if the course is often fatal In PMA steroid therapy has a very good palliative effect. Ophthalmological experience also suggests that steroid therapy has a good prophylactic and therapeutic effect. The two diseases also differ from one another in age and sex distribution Ac cording to Frohnert and Sheps (1967) in polyarteritis nodosa men are affected twice as often as women but in the present material of PMA the sex distribution was practically equal. The main age of polyarteritis nodosa (40—60 years) is lower than that of PMA.

It has been questioned whether Mb Buerger oc

curs as an independent disease, but recently isolated cases ha e again been reported (McKusick et al 1962, Brown et al 1968). According to these authors the disease shows a predilection for the arteries distal to the knee and elbow joints. The disease is rare, and it is generally agreed that smoking is a considerable predisposing factor Moreover this disease practically exclusively affects men. The histological changes are said to be different from those in giant-cell arteritis. Thus thrombus formation in the vessels appears to be more marked and the inflammatory changes in the vessel walls smaller in thromboangiitis than in giant-cell arteritis. Only one case of Mb Buerger was encountered during the period covered by the collection of the present material of PMA. That case was seen in a 35 year-old man who was a heavy cigarette smoker After abstinence from smoking and intense physical training the apical ulcers on the fingers and toes healed. In this connection it is worth mentioning that only one woman and three men of the 93 patients with PMA smoked more than 10 cigarettes per day

The most important problem is the relation between arteritic processes in PMA and the clinical symptoms and pathomorphology of arteriosclerosis (Chapters 9 and 10). In patients with mild inflammatory lesions it may sometimes be difficult to decide whether such changes are manifestations of primary arteritis or of a reaction to subintimal atheromatous plaques with or without calcium deposits. Gilmour drew attention to this difficulty as early as 1941 Atheromatosis and arteriosclerosis are not clinically or morphologically well defined terms either (Pickering 1963) Hamrin (1966) stressed that it must abide future clinical and pathologic investigations to find out to what extent stenosis of large and middle sized arteries are due to arteriosclerosis or to constricting and deforming healing processes after arteritis, or to a combination of both. The additional studies of the present large material of temporal arteritis and PMA suggest that postarteritic constriction is the most important cause of stenosis of large and middle sized arteries in the upper limbs. The possibility of arteriosclerosis obliterans being a sequelae after PMA should be borne in mind This also implies that ischaemic symptoms referable to the limbs and vascular damage to vital organs might be late sequalae after polymyalgia rheumatica dating many years back in the patients history The relation between PMA and arteriosclerosis deserves further investigation

Aneurysm of the aorta or large arteries has only been briefly touched upon in the present investigation, but such aneurysms are not uncommon in PMA. Occasionally such aneurysms have ruptured in the active phase of the disease, but when they rupture they generally do so several years after the onset of the disease.

This happened in the patient who died from a ruptured aneurysm 8 years after the onset of PMA (the patient was erroneously not included in the material). As in stenosis of large arteries and the aorta, one might very well imagine that a so-called arteriosclerotic aneurysm is in reality postarteritic. Inflammatory changes in the wall adjacent to a rupture or dissecting aneurysm is apt to be incorrectly ascribed to tearing and haemorrhage in the vessel wall, but they may instead be a manifestation of chronic primary arteritis.

HIGH ERYTROCYTE SEDIMENTATION RATE AND FEVER OF UNKNOWN ORIGIN

An extensive literature exists about fever of unknown origin (cf. Böttiger 1953 1956, Böttiger & Molin 1964). The presence of a marked and especially persistent elevation of E. S. R. without obvious reason is a common clinical problem (Liljestrand & Olhagen 1955 Olhagen & Liljestrand 1955 Ansell & Bywaters 1958, Zacharski & Kyle 1967). Chronic elevation of E. S. R. has been dealt with by Waldenström (1968) in his previously quoted monograph Monoclonal and Polyclonal Hypergammaglobulinaemia."

Bagratuni's anarthritic rheumatoid disease was discussed as possible pathogenetic factor for "unexplained" high E. S. R. by Ansell and Bywaters (1958) and for fever of unknown origin by Böttiger and Molin (1964). It seems reasonable to assume that PMA is one of the most frequent explanations for long lasting subfebrile temperature and elevated E. S. R. in middle aged and elderly patients. It is important to know that slight elevation of temperature may last for months and sometimes one year or more in PMA and a marked increase of E. S. R. may persist for more than a year and a moderate elevation can be present for many years in this disease.

It is generally accepted that E. S. R. increases with age This opinion received support by the study

of Böttiger and Svedberg (1967) in an apparently healthy population of working people This obser vation should, however raise the question wether the findings were influenced by the incidence of muscle rheumatism of minor degree This cannot be excluded, since such minor ailments as muscle pain are not generally accepted as a proper disease worth mentioning. The question is further substantiated by the finding of a parallel decrease in the haemoglobin concentration with ad ancing age

SUMMARY

For more than 20 years attempts have been made clinically to define a rheumatic disease, usually called polymyalgia rheumatica, and characterised by extra-articular symptoms, raised E. S. R. and predilection for the higher age groups. Such works are reviewed as is the discussion of the subject during the last decade concerning the clinical and pathological relations then claimed between the polymyalgic syndrome and temporal arteritis or giant-cell arteritis (Chapter 1).

In the present investigation the problem was approached on the basis of material of temporal arteritis and material of polymyalgia rheumatica. The former consisted of 46 systematically examined cases of temporal arteritis diagnosed at the department of internal medicine, Malmö general hospital, in 1952—1962, at a time before the problem had received serious attention in the literature (Chapters 12—14). The latter material consisted of 93 cases of polymyalgia rheumatica diagnosed in 1961—1968 on rigorously selected clinical grounds and examined prospectively at the department of internal medicine in Växjö (Chapters 2—11).

The chief criteria to be met for a diagnosis of poly myalgia were rheumatic symptoms of certain type and distribution and an E. S. R. above 50 mm/1 hr. Only patients above 50 years were included in the material. The patients were repeatedly and systematically examined with standardised methods for up to 8 years.

One of the main purposes of the investigation was to obtain as many biopsy specimens f arteries as possible for histological examination. Including two cases in which specimens were obtained only at autopsy arterial segments were obtained from 86 (92 %) of 93 cases. Arteritis was found in 51 (59 %) of the 86 histologically examined cases. The material was then divided into two series, one (A) consisting of 51 (55 %) cases of microscopically verified arteritis and one (B) consisting of 42 (45 %) without such confirmation.

Clinical analysis f the polymyalgic series lent support to the generally accepted view that in polymyalgia rheumatic symptoms are more severe and more obstinat in the region of the shoulder girdle than in the pelvic girdle. Nearly all the patients had fever usually protracted, and most f them lost many kilos in weight. The mean maximal E. S. R. in series A was 106 mm/1 hr and in series B 99 mm/1 hr Local and systemic symptoms wer somewhat more severe in series A than in series B.

The systemic routine clinical examination included measurement of the blood pressure in both arms. The Växjo material of polymyalgia included 14 cases of aortic arch syndrome In 9 patients of series A it can be stated with certainty that signs of aortic arch syndrome supervened in the course of their polymyalgic disease. Some large arteries of the patients were regularly auscultated at each examination. For comparison, 96 controls were examined in the same way The controls were age and sex matched but had no rheumatic symptoms t the examination or in their history The frequencies of cases with murmurs over the arteries xamined, and f cases with multiple murmurs were significantly higher in the patients than in the controls. About one third of the patients had stenotic murmurs over the main arteries to the arms, while no such murmurs were heard in the controls. Neither did aortic arch syndrome appear in any of the controls. Selective subclavian arteriography of 11 patients with murmurs over principal arteries to the arms with or without associated signs of aortic arch syndrome revealed in all xamined cases long stenoses of these arteries. The stenosis was usually most marked at the level f the origin of the subscapular artery and the posterior humeral circumflex artery

The patients were also compared with the controls regarding the results of haematomorphological and protein-chemical examinations of the blood and serologica studies. The patients showed tendency to anaemia f the same type as that seen in rheumatoid arthritis, tendency to leucocytosis, thrombocytosis and eosinophilia. Also these alterations were more marked in series A than in series B.

Of the 46 cases of temporal arteritis from Malmo, only histologically erified cases were after-examined. These 34 cases were compared with firmly diagnosed cases of arteritis in the Växjo material (series A). No significant differences were found between these materials regarding relevant clinical symptoms, except symptoms referable to the temporal region ($p < 0.01$). This difference only reflects the altered attitude to symptomatology in giant-cell arteritis.

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HIGH ERYTROCYTE SEDIMENTATION RATE AND FEVER OF UNKNOWN ORIGIN

An extensive literature exists about fever of unknown origin (cf Böttiger 1953 1956, Böttiger & Molin 1964). The presence of a marked and especially persistent elevation of E. S. R. without obvious reason is a common clinical problem (Liljestrand & Olhagen 1955 Olhagen & Liljestrand 1955 Ansell & Bywaters 1958, Zacharski & Kyle 1967). Chronic elevation of E. S R. has been dealt with by Waldenström (1968) in his previously quoted monograph Monoclonal and Polyclonal Hypergammaglobulinaemia.

Bagratuni's anarthritic rheumatoid disease was discussed as possible pathogenetic factor for "unexplained" high E. S. R. by Ansell and Bywaters (1958) and for fever of unknown origin by Böttiger and Molin (1964). It seems reasonable to assume that PMA is one of the most frequent explanations for long lasting subfebrile temperature and elevated E. S. R. in middle aged and elderly patients. It is important to know that slight elevation of temperature may last for months and sometimes one year or more in PMA and a marked increase of E. S. R. may persist for more than a year and a moderate elevation can be present for many years in this disease.

It is generally accepted that E. S. R increases with age This opinion received support by the study

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Morphological Changes in the Large Arteries in Polymyalgia Arteritica

by

GÖREL ÖSTBERG

MORPHOLOGICAL CHANGES IN THE LARGE ARTERIES IN POLYMYALGIA ARTERITICA

By Görel Östberg

Since the concept of temporal arteritis was introduced by Horton and Magath (1937) cases of arteritis with lesions in the aorta and other large arteries have been described by Barnard (1935), Sproul and Hawthorne (1937) and Gilmour (1941). Gilmour suggested that the disease should be called "giant-cell chronic arteritis," as the temporal arteritis appeared to be only part of a more widespread vascular disease. Harrison (1948) compiled data about temporal arteritis and he, too, stressed the disseminated nature of the changes in the large arteries. These and other earlier publications have been discussed in greater detail by Hamrin. Variations in the distribution of the lesions have been described by e. g. Frangenheim (1951) and Finlayson and Robinson (1955), who reported cases with lesions in the leg arteries and gangrene of the feet. An opinion that has gained ground in recent years and that is now generally accepted is that polymyalgia rheumatica is a variant of temporal arteritis with similar symptoms and organic changes, and lesions of the large arteries in polymyalgia have been described by e. g. Russel (1959), Alestig and Barr (1963) and Hamrin et al. (1965, 1968). The name polymyalgia arteritica is preferred by many authors as a more precise designation. The disease affects mainly elderly people of both sexes. Giant cells are often found in the arterial walls and are described as characteristic features. Takayasu's disease is arteritis, affecting mainly the thoracic aorta and the large arteries from the aortic arch, with circulatory disorders in the head and arms. It was first described in young women and has also been called "young female arteritis". — These two forms of arteritis are described in textbooks of pathology as different entities. The rarity of especially Takayasu's disease is mentioned, and is also apparent from the small number of published cases. Temporal arteritis is more common, although very little is known about its frequency in different populations. — The histological picture in biopsy specimens of temporal arteritis is well known, but the characteristics of lesions in the large arteries have not been described in detail. This is presumably because earlier publications concern very few personal cases and because it is not possible to obtain such a clear idea of the changes from descriptions as from personal examination. Gilmour (1937) described the gross and microscopical changes in 4 personal cases. Hamrin et al. (1968) reported 6 cases. An outstanding series of 72 necropsy cases, collected from several departments of pathology in Japan, was presented by Ueda et al. (1968). They stressed the most common gross changes, such as thickening of arterial wall, narrowing or obstruction of arterial lumen and oedematous thickening of the intima. — The histological changes were oedematous fibrosis in the intima and fragmentation of elastic fibers in the media and, possibly secondary thereto, diffuse fibrosis and chronic proliferative inflammation. Granulomata with necrosis and granulomata with giant cells were found, but were not a very prominent feature. The adventitia showed diffuse fibrosis and, sometimes, also narrowing of vasa vasorum.

A comprehensive survey of giant-cell arteritis, temporal arteritis and polymyalgia arteritica was published in the beginning of 1971 by Hamilton et al., who reviewed the lesions in the large arteries and stressed the characteristic histological features with cellular infiltration and destruction of elastica. — During follow-up of the clinical material of polymyalgia arteritica it was possible to obtain and study abundant material from different parts of the arterial system in a group of 14 cases of temporal arteritis and polymyalgia arteritica and two cases of polyarteritis nodosa.

MATERIAL AND METHODS

The investigation comprises two parts, namely an analysis of the patients who had died in the material followed-up clinically and a systematic study of the large arteries in a group of patients with arteritis, half of whom belonged also to the former series. These two groups are summarised in Tables 1 and 2. — Of the 127 patients followed-up clinically 36 died before the end of 1970, and all together 27 of them were necropsied. Six cases were reported by Hamrin et al. (1968). Concerning the

Case nr	Syst nr	Sex	Age (death)	Temp. biopsy	Inter val	Main cause of death	Arteritis at necropsy
2		F	73	+	8	Infarctus myocardii	
5		M	75	+	2	Cancer maxillae	
6	×	M	74	+	3	Cancer prostatae	+
14		M	65	+	6	Infarctus myocardii	
23		F	68	+	4	Gangraena intestini	+
24		F	73	—	7	Infarctus pulmonis	—
26	✓	F	74	+	3	Cancer coli	+
30	✓	F	77	—	3	Infarctus cerebri	—
33	×	F	65	+	1	Haemorrhagia cerebri	—
34	XIII	F	76	+	15	Cardiosclerosis	+
37	III	M	82	+	4	Infarctus pulmonis	+
39		M	71	—	2	Gangraena cruris	—
43	✓	F	64	—	7	Pancreatitis acuta	+
48		M	78	+	/	Infarctus myocardii	
49	✓	F	74		5	Gangraena intestini	+
81	IV	M	73	+	1	Infarctus pulmonis	+
91		M	71		2	Infarctus cerebri	+
101		M	87		15	Amyloidosis	+
102		F	71	+	6	Suicide	
103		F	72		8	Infarctus cerebri	+
104		F	77	+	11	Cardiosclerosis	
105		M	76	+	1	Cardiosclerosis	
106		M	83	+	10	Cancer recti	
107	XIV	F	77		14	Bronchopneumoniae	+
108		M	43		10?	Morbus Takayasu	+
109		F	60	—	1	Infarctus myocardii	+
111		M	73		5	Infarctus myocardii	+
113	II	F	82	+	7	Cardiosclerosis	+
113		F	75	+	4	Uraemia	—
115		F	83	+	4	Ulcus ventr. c. haemorrh.	+
120		F	83	+	4	I farctus myocardii	
121		M	77	+	2	Carcinoma coli	+
122	I	M	69	+	7	Infarctus cerebri	+
123		F	77	+	2	Infarctus myocardii	+
129	IV	F	72	+	9	Infarctus myocardii	+
134	XII	F	17		2	Morbus Takayasu	+

Table nr 1. All deaths in clinical material. Syst. nr indicates cases in series studied systematically given Roman numerals.   in this column indicates series published earlier by Hamrin et al (1968). Interval denotes interval in years between onset of symptoms and death.
+ arteritis or sequelae after arteritis
— no arteritis
  no investigation

9 who were not necropsied and the 13 not systematically studied, information was obtained from the death certificates and the necropsy protocols. Tissue for microscopic examination had been obtained from the large vessels in most of the cases, but the material was scanty and therefore not suitable for any detailed analysis. The findings appear in Tables 1 and 2.

The group examined systematically consisted of 16 cases. To distinguish these from the clinical series they were given Roman numerals. Cases I—VI belonged to Hamrin's material (Case V was, however excluded from the clinical material after a primary examination because of the difficulty in excluding other complicating disease, see page 77). In Cases VII, VIII and IX temporal arteritis had been diagnosed clinically or histologically some years before death. — No disease had been previ

Syst nr	Case nr	Sex	Age (death)	Clin. diagn.	Temp. biopsy	I ter al	Main cause f death
I	122	M	70	Temp. arteritis	+	6	Infarctus cerebri
II	113	F	83		—	8	Cardiosclerosis
III	37	M	83		+	4	Infarctus pulmonis
IV	81	M	74		+	1	Infarctus pulmonis
V	—	F	65		—	7	*Ruptura aortae*
VI	129	F	73		+	9	Infarctus myocardii
VII	—	M	71		+	4	Infarctus cerebri
VIII	—	F	78		+	3	Infarctus myocardii
IX	—	F	74			3	Cancer bronchialis
X	—	F	86	VOC incomp		2?	Aortitis. Bronchopneumoniae
XI	—	F	88	Cardiosclerosis		9?	Cardioscleros. Dilatatio aortae
XII	134	F	17	Mb Takayasu		2	Infarctus myocardii. Morbus Takayasu
XIII	34	F	76	Cardiosclerosis	+	15	Cardiosclerosis
XIV	107	F	78	Mb Takayasu		14	Cardiosclerosis. Bronchopneumoniae
XV	—	F	67	Polyart. nod.		2 mths	Polyarteritis nodosa
XVI	—	F	56			3 mths	Polyarteritis nodosa

Table nr 2. Cases studied systematically denoted by Roman numerals. Case nr = nr in series followed clinically Interval = time in years between onset of symptoms and death.
+ arteritis diagnosed in biopsy specimen
— no arteritis
no investigation

ously diagnosed in Cases X and XI but necropsy revealed suspect arteritis of the aorta and large arteries and microscopic examination confirmed the diagnosis. — Case XII belonged to the group followed-up clinically The patient died in 1964 and necropsy specimens had not been obtained to the same extent as in the other cases. — Case XIII came from the series followed clinically but was necropsied elsewhere. Different parts of the arterial system were studied, not quite as extensively as in cases I—XI Case XIV was also examined less extensively for reasons given below — Cases XV and XVI had had clinically known polyarteritis nodosa the large vessels in these cases were examined in the same way as in the rest of the material in order to permit comparisons between the various arterial diseases.

The arteries were obtained t necropsy and fixed in eutralized formalin. The entire aorta was rem ved, the carotid arteries were excised to the base of the skull and often also the basal cerebral arte es were examined. As a rule, the temporal arte ies were studied. The subclavian and arm arteries were removed to the level of the elbow abdominal and renal arteries, a few centimeters after their origins and leg arteries, to the level of the knee. In most cases the coronaries were also examined. — Transverse sections 1—3 cm apart were taken for histological examination. As a rule, then, one section was examined for every 2 cm, from the origin of the aorta to the region of the elbow and knee, respectively For various reasons the extent of the material obtained varied from case to case, the number of transverse sections examined in the different regions is given in Table 3 17—175 sec

Case nr	Aorta	Rarm	Rcar	Lcar	Larm	Rleg	Lleg	Total
I	13	6	22	23	23	35	21	172
II	13	30	13	14	28	18	21	137
III	15	28	11	12	27	24	27	144
IV	*9*	*11*	*4*	*4*	*11*	*8*	*8*	*55*
V	15	30	10	9	28	24	23	139
VI	14	35	6	6	43	33	38	175
VII	12	33	18	11	30	29	29	162
VIII	15	16	6	9	13	23	27	109
IX	9	6	6	7	5	25	24	82
X	4	5	15	11	3	8	4	50
XI	4	4	15	6	10	0	0	39
XII	3	4	3	3	4	0	0	17
XIII	5	8	5	12	6	4	3	33
XIV	0	44	0	0	33	0	0	77
XV	9	7	6	6	3	11	10	52
XVI	8	22	7	7	17	22	22	106

Table nr 3 Number of sections from different arteries, aorta, right arm, right carotid, left carotid, left arm, right leg, left leg.

Case r	Syst nr	Sex	Age (death)	Temp. biopsy	Inter val	Main cause of death	Arteritis at necropsy
2		F	73	+	8	Infarctus myocardii	
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113	II	F	82	+	7	Cardiosclerosis	+
113		F	75	+	4	Uraemia	—
115		F	83	+	4	Ulcus ventr c. haemorrh.	+
120		F	83	+	4	Infarctus myocardii	
121		M	77	+	2	Carcinoma coli	+
12.	I	M	69	+	7	Infarctus cerebri	+
123		F	77	+	2	Infarctus myocardii	+
129	IV	F	72	+	9	I farctus myocardii	+
134	XII	F	17		2	Morbus Takayasu	+

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+ arteritis or sequelae after arteritis
— no arteritis
no investigation

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N	Temp		Coronary			Pulm	Coeliac	Mes sup	Renal		Muscles	Organs
	R	L	R	Ld	Lc				R	L		
I	+	+	+	—	—	—	—	—	—	+	—	—
II	+		—	—	—		—	—	—	—	—	—
III	+	+	—	—	—		—	—	+	—	—	—
IV	+	+	—	+	—		—	—	—	—	—	—
V		+	+	—	—	—	+	+	+	+	—	—
VI			—	—	—		—	—	—	—	—	—
VII		+	—	—	—		—	—	—		—	—
VIII			—	—	—	—	—	+	—	—		—
IX	+	+	—	—	—		—	—	—	—		—
X		+	—	—	—		—	—	—	—		—
XI	—	—	—									—
XII		—	+						—			—
XIII	+	+							—	—		—
XIV	+	—	—	—								—
XV	—	—	—	—	—		—	—	—	—	+	+
XVI			—	—	—		—	—	—	—	+	+

Table nr 4. Arteries, not included in diagrams. Temporal arteries, (right and left) coronaries (right, left descending, left circumflex), pulmonary coeliac, superior mesenteric, renal (right and left). Muscles from arms, legs, pectoral, psoas.

\+ arteritis or sequelae after arteritis
— no arteritis
no investigation

Fig. 2. Case I. Thoracic aorta with large branches. Thickened wall with thick, glossy intima of the arch. Advanced atheromatosis with ulcerations in the descending aorta. Both subclavian arteries widened proximally in the right, mural thrombus (double arrows) situated 20 cm from its origin in the left, an occlusive thrombus (arrow) about 12 cm from its origin, distally thereto 3 cm long segment of normal appearance, followed by 2.5 cm long thrombus. Brachial and carotid arteries of normal width with smooth walls. In the left internal carotid an occlusive thrombus.

sea after infarction. — Most of the right cerebral hemisphere was soft and disintegrating with gray yellow discoloration. The left part of cerebellum showed similar necrosis. — The lower lobes of the lungs contained partly coalescent foci of bronchopneumonia.

Microscopic findings. The aorta and large arteries showed pronounced intimal thickening with collagen tissue, poor in cells, and areas of amorphous material with fat vacuoles and deposits of blood pigment in deeper parts of the intima. In these areas the media was thin and small groups f lymphocytes, plasma cells and histiocytes were seen along capillaries, which penetrated into the media. In some areas the media showed *patchy necroses with no nuclei and with* coarse elastic lamellae with increased eosinophilia. Ad-





Fig. 3 Case II. Thoracic aorta. Mild proximal widening, thickened, wrinkled, glossy intima.

jacent to these necrotic foci were some multinucleated giant cells and a few round cells. The adventitia showed widespread fibrous thickening, poor in cells with small accumulations of lymphocytes around capillaries.

Cause of death. Extensive brain infarction because of thrombosis of the left internal carotid artery

CASE II (0 616/68). A woman, born in 1885. In 1960 she had had temporal arteritis, not histologically verified. She was treated with steroids for some months. — From 1964 she had increasing senile dementia with confusion and occasional abdominal pain and died after general deterioration in June, 1968.

Fig. 4 Case II. Left arm artery. Stenosis (right arrow) 7 cm and (left arrow) 17 cm from its origin.

NECROPSY

Gross findings. Slight widening of the proximal aorta with generalised intimal thickening and longitudinal and transverse wrinkling (Fig. 3). Practically no changes of arteriosclerotic type. Slight narrowing of the right arm artery 7 cm from its origin (distally in subclavian artery) with wrinkling of the intima, and after 18 cm (distally in axillary artery), further narrowing within a limited segment. The left arm artery showed slight narrowing after 7 cm and after 17 cm (Fig. 4). The carotid arteries appeared normal. — The heart was of normal size and configuration, mild arteriosclerotic changes were found in the coronary arteries. — The lungs were heavy and congested, the liver and spleen were rich in blood.

Microscopic findings. Widespread necroses of the media of the aorta with coarse and fragmented elastic lamellae. Vessels from the adventitia penetrated into the media, partly towards the slightly thickened intima. Around these vessels were abundant round cell infiltrations. In the subclavian and arm arteries the



elastica was thin and partly fragmented with only mild cellular reaction (Fig. 7). — Proximally in the iliac arteries were areas of disintegrated and coarse elastic lamellae with slight cellular reaction.

Cause of death. Cardiac incompensation

CASE III (0 V 1/68). A man, born in 1885 Admitted to hospital in 1961 because of fever with exanthema, headache and dizziness, symptoms which were interpreted as cerebral circulatory failure and urinary tract infection. — In 1964 he had polymyalgia arteritica with right-sided headache and pain in the shoulder and pelvic girdles. Biopsy of temporal artery showed arteritis. He was treated with steroids in small doses for about a year 1964—65 Multiple murmurs and transient pulselessness of the left radial artery were found. Roentgen examination showed long stenotic sections of the left subclavian artery After gradual deterioration of his general condition the patient died in June, 1968 (for further information see Hamrin page 91).

NECROPSY

Gross findings. Aorta and its branches were moderately changed with sparse, partly calcified lipid plaques Particularly the thoracic aorta showed thin, longitudinal and transverse wrinkling of the intima. In the left arm artery 20 cm from its origin from the aorta (distally in axillary artery), the lumen was stenosed to circumference of about 6 mm, proximally thereto 11 mm, distally 13 mm. A similar though much less marked, narrowing was seen in the corresponding part of the right arm artery The carotid arteries were tortuous and partly converted into calcareous tubes. — The heart was somewhat enlarged with predominance of the left ventricle, the coronaries were stiff and calcified with lumina of normal width. The myocardium of the left ventricle contained few fibrous scars about half a centimeter in diameter — Thrombi were found in the left deep femoral vein and abundant thrombo-embolic masses in both of the main branches of the pulmonary artery The lower lobes of the lungs contained foci of bronchopneumoniae. — Microscopic examination revealed latent prostatic carcinoma

Microscopic findings Widespread, irregular patchy destruction of the media of the entire aorta, of both arm and carotid arteries and proximal parts of the iliac arteries (Figs. 8 11 12). Scattered giant cells. Mild, diffuse intimal thickening with fibrosis, poor in cells, in some areas with fat vacuoles deep in the intima. Mildly thickened dense adventitia with normal vasa vasorum.

Cause of death Pulmonary embolism. Brochopneumoniae.

CASE IV (0 V 2/68). A man, born in 1894 H suddenly fell ill in August, 1967 with headache on the left side mainly in the back of the head. Biopsy of the temporal artery showed arteritis. Steroid therapy (August, 1967—October 1968) produced clinical improvement with decreasing E. S. R. from 100 mm/1 hr I October 1968 fter having been in hospital for 14 days, he died with symptoms of pneumonia.

NECROPSY

Gross findings. The aorta was of normal width with scattered soft fibrous plaques, no wrinkling or calcium deposits, branches of normal width with smooth walls. — The heart was markedly enlarged particularly the left ventricle. The aortic ostium was stenosed with partly adherent, fibrotic valves. The coronaries were wide and showed thin atheromatous plaques. — The left femoral vein and its branches were filled with red-brown dry thrombic masses and the larger branches of the pulmonary artery contained several partly old thrombo-emboli Widespread pulmonary infarcts were seen, one in the left lower lobe was the size of fist and undergoing liquefaction. — The brain arteries showed marked sclerosis and there was an old infarction in the left frontal lobe and a walnut-sized softening in the left occipital region. — Bronchopneumoniae were seen in the lungs.

Microscopic findings Aorta and its large branches had relatively small streaks of necroses in the media with collapsed elastic lamellae. I widespread areas there was mild, oedematous loosening, with diffuse deposits of lymphocytes and plasma cells between preserved elastic lamellae and smooth muscle cells (Fig. 5). A few giant cell granulomas were found and there was moderate thickening of the intima with streaks of connective tissue poor in cells, in some areas f t vacuoles and deposits of blood pigment.

Cause of death Pulmonary emboli and infarcts.

CASE V (0 V 1/69). A woman, born in 1904 She had had long standing, obscure disease with fever in the beginning of the sixties and arteritis was suspected Later examination revealed tuberculosis of the cervical lymph nodes and the systemic symptoms were thought to be due to tuberculosis. Roentgen examination in 1963 had shown an aorta of normal width, re examination in 1968 pronounced widening of the thoracic aorta. Admitted for investigation and possibly operation of an aortic aneurysm, she suddenly died in September 1969 after acute haemoptysis

NECROPSY

Gross findings Already at its origin the aorta was widened and its wall was thin and showed scattered, thin calcium deposits and mild wrinkling of the intima. 10 cm distally to the aortic arch was an aneurysm almost the size of a child's head bulgi g into the



Fig. 5 Case IV Aorta at the bifurcation. Outer part of the media with ad entitia down to the right. I the left upper part the structure of the media is preserved with thin, elastic lamellae and elongated nuclei. The outer part of the media in the middle of the picture is oedematous with diffuse round-cell infiltration. A wide, blood-filled capillary is seen (arrow). The elastic la mellae are preserved There are some round cells in the adventitia Haematoxylin — eosin x 51

lower lobe of the left lung, with rupture nd diffuse bleeding into the lung. The aneurysm had a sharp lower border the abdominal aorta was generally widened and had a rather thin wall. Distally to the renal arteries was a 2 4 cm mural thrombus. The iliac ar teries were of normal width, annular calcifications of the type seen in Monckeberg-sclerosis were found in the distal parts of the femoral arteries. — The heart was of normal size and configuration and the coronary arteries were of normal width with scattered, soft or slightly calcified plaques.

Microscopic find ngs The aortic w ll was thin, the elastica wa destroyed in large areas and partly replaced by connective tissue poor in cells (Fig. 9). Dense foci of lymphocytes and plasma cells were found in the media and in the adventitia. The intima showed fibrotic thickening, partly with fat deposits and blood pigment. Arteritis ith patchy medial necroses was seen in the femoral arteries (Fig. 10). Here some giant c lls were found. Distally there were calcified and ossified streak in the media as in Monckeberg-sclerosis.

Cause of death Aortitis ruptur of aortic aneurysm

CASE V I (0 258 70) A woman born in 1897 She had had symptoms of polymyalgia rheumatica in 1961 when biopsy of the temporal artery had shown arteritis. She was treated with steroids in small doses until her death. — In 1967 she had venous thrombosis of the lower leg. — In February 1970 she suddenly fell ill with a clinical picture and laboratory values compatible with myocardial infarction. She died three weeks later

NECROPSY

Gross f nding The aorta was slightly widened with diffuse fine wrinkling of the intima along its entire length a well as scattered pale yellow plaques about the size of a thumb-nail partly calcified and partly ulcerated. A 2 / 2 cm mural thrombus was found immediately after the origin of the renal rteries, more widespread thrombic deposits further distally Moderat thickening and wrinkling of the intima was seen in the arm arteries, which were of normal width. The proximal part of the left iliac artery was slightly widened and filled with dense organised pale yellow thrombi. — The heart was somewhat enlarged but of normal configuration. The right coronary artery was occluded by a thrombus and in the posterior and lateral walls of the left ventricle wa an infarct under going resorption.

Microscopic findings Proximally in the aorta and arm arteries were widespread, irregular patchy medial necroses with round-cell deposits marginally and scattered giant cells (Fig. 13). Distinct changes were seen n small branches of the iliac arteries and in the femoral rteries. Especially in the aorta the intima was

thickened with inwardly bulging, cushion-like foci of connective tissue.

Cause of death. Myocardial infarction.

CASE VII (0 S 196/68). A man, born in 1897 I December 1964 he had acute onset f fever and pain in the right temple, biopsy showed temporal arteritis, hich promptly responded to steroid treatment, which as continued for some months. In 1967 he had an acute, right-sided hemiplegia, from which he did not improv and he died in June, 1968.

NECROPSY

Gross findings. The aorta was of normal width with thickened intima throughout its length with peculiar mother-of-pearl-like appearance and diffuse, mainly longitudinal wrinkling. There were scattered yellowish lipid plaques, with calcifications in the distal part. The proximal parts of the arm arteries were slightly widened with intimal thickening; in the right, after 10 cm (distally in subclavian artery), there was considerable narrowing; in the left, mild narrowing. — The heart was rather small and of normal configuration. — The left femoral vein contained partly mural thrombi the right pulmonary artery thrombo-emboli. — Widespread bronchopneumoniae with liquefaction were found in all lung lobes. — The major part of the left brain hemisphere was in state f liquefaction with yellowish discoloration of its margins.

Microscopic findings. Patchy medial necroses were seen in the aorta and its larger branches. Scanty round-cell infiltration and some vascular ingrowth was found around necrotic areas. There was pronounced intimal fibrosis with cushion-lik thickening.

Cause of death. Cerebral infarction, bronchopneumoniae.

CASE VIII (0 293/70). A woman, born in 1892. She had been treated for hypertension since 1964 In 1967 she had had histologically verified temporal arteritis and was treated with steroids for some months. — In March, 1970 she had sudden onset f symptoms compatible with myocardial infarction and she died two week later

NECROPSY

Gross findings Moderate longitudinal wrinkling of the aortic intima was found. Proximally scattered, distally coalescent, yellow-white plaques were seen with ome calcified parts distally — The heart was of norm l size and conf guration, the coronaries had becom narrow calcified tubes and the posterior wall of th left entricle showed recent infarction with per f ration and haemopericardium.

Microsc pic findings. The distal aorta showed small medial necroses with round-cell deposits and capillary proliferation, no true destructions of the elastic lamellae ere seen. Patchy medial necroses were found proximally in the subclavian arteries, pronounced medial changes with necrosis, round-cell deposits and a fair mber f giant cells in the leg arteries. I several areas the intima was very thin and smooth, slightly raised foci consisting f connecti tissue rather poor in cells w re found. Other areas showed hyaline streaks with fat vacuoles. The coronaries showed changes, suggestive of arteritis.

Cause of death. Myocardial infarction.

CASE IX (0 505/70). A woman, born in 1896 I 1967 she had had temporal arteritis, not verified histologically She had not received steroids. She complained of fatigue, loss of weight and feeling of heaviness in the right half of the chest in the spring of 1970, and died in May 1970.

NECROPSY

Gross findings The aorta was of normal width with slight intimal wrinkling, especially in the ascending part. The large branches from the aortic arch were somewhat widened with thickened, mildly wrinkled intima Scattered, yellow-white, partly calcified foci, about 5 mm in diameter were found proximally in the abdominal aorta. — The heart was f normal size and configuration. — The lower lobe of the right lung contained fist-sized tumour (small-cell, anaplastic carcinoma) with metastases in the liver and adrenals.

Microscopic findings. The aorta and its larger branches contained scattered, irregular almost reactionless medial necroses and small infiltrates with lymphocytes and plasma cells were seen in the media and adventitia (F g. 6). Some sections showed mild medial oedema with capillary ingrowth and sparse round cell streaks. The intima was diffusely thickened with hyaline streaks and small f t deposits. One branch, about 1 mm in diameter of the femoral artery showed an rea f mural necrosis with round cell deposits.

Cause of death. Bronchial carcinoma.

CASE X (0 909/68). A woman, born in 1882. Her left breast was amputated in 1930 but no malignant lesion was found. — In 1966 she was admitted to hospital because of cardiac incompensation and again later that year because of myocardial inf rction (anterior and posterior wall). In 1967 she was again admitted because of cardiac incompensation, presumably due to ombined aortic stenosis and insufficiency She died from heart failure in August, 1968.

NECROPSY

Gross f ndings. The proximal part of the aorta was markedly dilated with insufficiency of the aortic valve. The al e leaflets were somewhat thick, but of normal



Fig. 10 Case V Deep femoral artery Media, in the upper part thickened intima, in the lower part adventitia. The internal elastic lamina is preserved (arrow). The media contains granulomas with histiocytes and giant cells around small calcifications. Abundant deposition of round cells. Preserved muscular media below granuloma (arrow) outside of which is adventitia with coarse collagenous and elastic lamellae. Htx — eos. 51



Fig. 11 Case III. Middle part of the left common carotid artery Entire arterial wall, intima upwards shows moderat thickening and streaks of pale fat macrophages. To the right (arrow) medial necrosis with coarse partly loose ed elastic lamellae and no nuclei. In the margin [illegible] necrosis round cell infiltration. Collections of [illegible] cells around capillaries in the adventitia [illegible] 20.



Fig. 12. Close-up view of the former picture with nec rotic media to the right and giant cells in the middle. Htx — eos. x 128

sue The vasa vasorum were of normal appearance with thin walls and no signs of narrowing, obliteration or inflammation.

Changes, noted in diagrams, were typical me dial necroses or pronounced round cell infiltrations, cellular intimal thickening and marked, diffuse, ad entitial fibrosis. Any change in a transverse section of the artery was marked as positive. The lesions were not coalescent in the areas marked.

No arterial lesions were seen in the organs exa mined or in the skeletal muscles, except in the cases of polyarteritis nodosa (XV XVI). The joints were not examined.

In cases with clinical or histologically erified polyarteritis nodosa (XV XVI) small arteries up to 1 mm in diameter showed changes in the form of fibrinoid necroses with accumulations of poly morphonuclear leucocytes and some round cells. These fibrinoid necroses were seen in the vasa vasorum of larger arteries, but no lesions were found in the corresponding parts of the large ar teries. These two cases (XV XVI) were therefore not inserted in the diagrams.

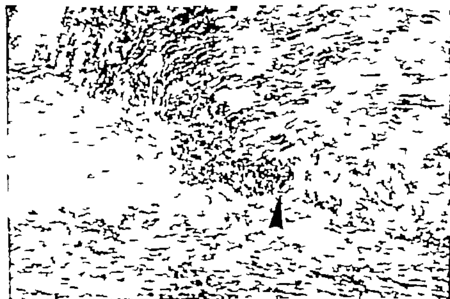


Fig 13 Case VI Aortic root. Media, intima above, d entitia below The upper right hand corner show necrotic media with coarse lamellae and destroyed nuclei. Around rupture in the necrotic media granulation tissue with capillaries, histiocytes and lymphocytes, one giant cell (arrow). The lower margin shows preserved outer part of the media with wavy elastic lamellae and thin nuclei. Htx — eos. x 75



Fig 14 Case XII Left subclavian artery The entire arterial wall with lumen up to the right. Preserved media with normal elastic structure. Marked thickening of the intima with cushion-like projection into the arterial lumen of loose tissue with some collagenous bundles and streaks of smooth muscle cells. Adventitia t the lower margin is normal. Htx — eos. x 75

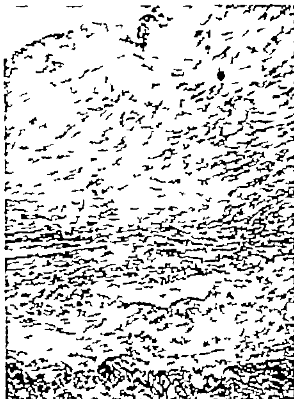


Fig 15 Case XII Right subclavian artery Inner part of arterial wall, lumen up to the left. Pronounced intimal thickening with loose tissue with fibroblasts and smooth muscl cells, some collagen bundles. Wide recanalisation lumen in the basal part. Preserved internal elastic membrane in the lower margin, a defect with fibrosis and a capillary in the left part (arrow). Htx — eos. x 75



Fig. 16. Case XII. Descending aorta. Outer part of the arterial wall, intima above, adventitia below. The media is thin, the dark areas to the right and left are necrotic parts with remnants of coarse, elastic lamellae and destroyed nuclei. Capillaries, surrounded by a few lymphocytes, are growing into the defect. The intima is thickened with fibrous tissue poor in cells, and numerous fat vacuoles (theroma). Marked dense fibrosis in the adventitia in the lower margin. Htx — eos. x 20.

DISCUSSION

COURSE OF POLYMYALGIA ARTERITICA AND CAUSES OF DEATH

The patients followed clinically fell ill fairly late in life (57—79 years) and lived to an old age (60—87 years) with but two exceptions, one man and one woman, who died at 43 and 17 years, respectively after an illness of uncertain duration The histories and courses have been discussed by Hamrin — The series consisted of 21 women and 15 men, which does not mean a significant difference in sex distribution — The two youngest patients died from arteritis with myocardial infarction In none of the other cases could arteritis be regarded as the main cause of death. — 19 patients were necropsied under varying circumstances. Signs of arteritis were found at histological examination in 14 none in the remaining 5

The six patients who had arteritis of the large arteries in the series studied systematically who *were not in the material followed up clinically* belonged to the older age groups (65—88 years), the two patients who had polyarteritis nodosa were 67 and 56 years, respectively In three cases arteritis was the main cause of death, in one as a result of rupture of a large aneurysm in the thoracic aorta (V), and in two (X, XI) as a result of dilatation of the aorta and, to some extent, of the aortic val e, resulting in cardiac failure. The two last-mentioned patients had no earlier history of polymyalgia arteritica, but had had vague symptoms for ⌞ and 9 years, respectively Thus, there was no case of acute death from arteritis, but four patients died from arteritis, including the young woman with Morbus Takayasu

Temporal arteritis is a disease of the elderly the prognosis is evidently good with few deaths in the acute stage. In the material studied systematically the duration of the disease was 1 to 15 years. Two f the patients with arteritis as a direct cause of death had been known to have had the disease for 2 and 7 years, respectively the other two had not been followed up. The changes found at necropsy probably reflect a late stage of the disease.

Deaths, caused directly by arteritis with dilatation f the aortic ostium have been described by g Clark et al (1957) I their cases, however the valves were changed by endocarditis, which was not seen in our cases. Their cases also had widespread manifestations of rheumatoid arthritis with spondylitis Harris (1968) described aortitis with dissecting aneurysm and rupture of the ascending aorta in two patients Garret (1962), a similar case *with the report of 6 earlier cases, and one has* been described as one of the Case Reports from *Massachusett s General Hospital" (1971) Aneu*rysmal rupture has also been described in children g by Wagen oort et al. (1963). Aneurysms of the aorta have been operated upon with success (Kent & Arnold, 1967). Gilmour (1941) reported a case of rupture of an aneurysm of the subclavian artery

In one of the cases (I) the cause of death was cerebral infarction, secondary to thrombosis of the internal carotid artery in a 70 year old man. Such a lesion is not uncommon in arteriosclerosis, but the artery showed typical microscopic changes and a causal relationship between arteritis and death seems probable A similar case with arteritis and cerebral ischemia has been described by Cardell and Hanley (1951).

Involvement of the coronaries may have more *serious consequences than changes in the peripheral arteries* This is illustrated by one of the patients, *the girl of 17 (XII) and also by the man of* 34 in the clinical material In the case described by Cardell and Hanley (1951) the patient had two old myocardial infarctions and the authors doubted that these could have been caused by arteritis because they occurred 7 and 13 years, respectively before death. However the coronaries showed arteritis and, with knowledge of the chronicity of the disease, the relationship sounds quite possible. Further cases with involvement of the coronaries ha e been described by Shrire and Asherson (1964).

THE ANATOMIC CHANGES

Gross findings

Arteritis can not be diagnosed with certainty from the gross findings at necropsy In two cases (X, XI) with marked dilatation of particularly the prox mal aorta, however arteritis was strongly suspected, although the patient s records contained no information about chronic arterial disease The diagnosis of arteritis was verified microscopically In these two cases, as in all together more than half of the material, the intima of the arteries was thickened and had a pearly appearance. The intima also showed a distinct, diffuse, fine or coarse wrinkling. Pearly thickening and wrinkling had been emphasised already by Gilmour (1941) and by several

other authors. In a *few* cases there were thin reddish deposits on the aortic intima resembling those described by Gilmour (1941) and Frangenheim (1951). They did not look like ordinary thrombi. Mural, dark-red thrombi were found in the abdominal aorta in two cases, resembling the thrombi seen in some cases of pronounced atheromatosis. In four of the cases the arm arteries showed changes, which appear strange (though in vessel segments not examined routinely at necropsy) in the form of partial or complete narrowing between 10 and 20 cm from the origin of the subclavian artery from the aortic arch, in the proximal or distal part of the axillary artery. This is an interesting observation in agreement with the murmurs heard over the axillary arteries. No changes suggestive of arteritis were found in other large arteries.

Microscopic findings

The diagnosis of arteritis is based on tissue changes, observed at microscopic examination. The typical picture of *acute temporal arteritis* consists of oedema or fibrinoid necrosis of part or all of the arterial wall with narrowing of the lumen. Inflammatory cells are found in varying amounts, in some cases polymorphonuclear leucocytes, but mostly round cells and histiocytes, and often multinucleated giant cells. The internal elastic lamina is usually destroyed. As has *previously been shown by Ainsworth* et al. (1961), Lie et al. (1970) and Östberg (1971), *arteritis leaves behind recognisable changes* in the form of narrowing of the artery, intimal thickening, splitting up or destruction of the elastica and more or less pronounced fibrous thickening of the adventitia. According to Bevan et al. (1968), the intimal fibrosis, which might be interpreted as a sign of healing may, however, also be seen in the acute stage.

The large arteries did not show any signs of acute arteritis, there were no fibrinoid necroses and no inflammatory reactions of acute type with leucocytosis. The known clinical course of the cases in this material does not allow any definite conclusions about the development of the arterial lesions. According to descriptions given by other authors, no typical acute stages have been found. Frangenheim (1951) described a 7? year-old man with diffuse "rheumatoid disease" since two years and general deterioration since 5 months. He found a diffuse inflammatory destruction of the media of the aorta and arteries, most pronounced in the proximal parts, with histiocytes and giant cells but also some polymorphonuclears. The inflammation subsided in the distal artery branches in the organs. The changes were mainly those of chronic, granulomatous inflammation. Lander and Bonnin (1956), described a case of arteritis with a relatively dramatic course, in which the patient, a 75 year-old woman, died within less than one month of the onset of temporal headache, followed by sudden blindness. The patient died from acute pulmonary embolism. Necropsy revealed signs of advanced arteritis of the large arteries with destruction and abundant infiltrates of lymphocytes, plasma cells and multinucleated giant cells in the media and adventitia. Only small groups of polymorphonuclear leucocytes were found and the picture was obviously the same as in cases with a more chronic disease. But, according to the patient's history, the woman had for many years had "mild arthritis of rheumatoid type," which may have masked polymyalgia arteritica. In the second case of Sproul and Hawthorne (1937), in a 50-year-old man, the media of the aorta showed diffuse infiltration of plasma cells and multinucleated giant cells. Here, too, then the inflammatory infiltrate was of a chronic type, though the changes were evidently diffuse. This patient had not had any previous symptoms of temporal arteritis or polymyalgia.

In three of the cases (IV, VII, X) there was a moderate, rather diffuse oedema in the *media* with loose infiltrates of lymphocytes. It could give the impression of being a rather acute affection. Another, more characteristic medial lesion, occurred in varying degree in all cases. It consisted of more or less widespread, *patchy necroses in the media* with destruction of the elastic lamellae. It was found in the aorta and large arteries. It has been described as primary and characteristic by Kimmelstiel et al. (1952) and has been stressed in Japanese investigations by Ueda et al. (1968), while other authors, *e.g.* Heptinstall (1964) only casually mention the changes in the elastica and stress the more diffuse inflammatory changes in the media.

Harrison (1948) stressed necroses of smooth muscle nuclei in the media and felt that the destructions in the elastic lamellae were small and less prominent. An investigation, lending support to the assumed role of the smooth muscle nuclei was that

by Reinicke and Kawubara (1969), who on electron microscopic examination of biopsy specimens of temporal arteries found that the primary change consisted of degeneration and necrosis of the smooth muscle cells in the media with secondary destruction of the elastic lamellae, which they believed to be formed from the membranes of the smooth muscle cells. Judging from the present series, medial necroses are the primary lesion, but it can not be determined whether they start by destruction of nuclei or elastic lamellae. The oedematous changes in the media might be a pre-necrotic stage. The necroses were sometimes strikingly reactionless and fairly well outlined against surrounding preserved elastica, which showed thin wavy lamellae and elongated nuclei. Adjacent to interruptions of necrotic media dense infiltrates of round cells around ingrowing capillaries could be found. This might be interpreted as an organisation and resorption of the necrotic tissue. Varying numbers of multinucleated giant cells of foreign body type were found around the broken elastic fibers. They did not appear to be an obligatory accompaniment, but rather a nonspecific reaction to the destruction of the media. Giant cells could develop as a result of a fusion of histiocytes. The above mentioned electron microscopic investigation by Reinicke and Kawubara (1969) lent support to the same view about the giant cells. The non-specific role played by the giant cells has been stressed by Gilmour (1941) and Hamperl (1953) and also by Isaacson (1961). It might therefore be questioned whether the term giant cell arteritis should be retained. But it is widely used, it is deep-rooted in the literature, it designates a relatively uniform clinical picture and it is difficult to find better name. Its use will therefore presumably continue unchallenged although, like Crosby and Wadsworth (1948), I would prefer the term "temporal arteritis" with the implication that it is a more or less widespread disease of the large arteries. As for the localisation in the artery wall both the diffuse oedema and round cell infiltration, suggestive of an early stage, and necroses, suggestive of a later stage, generally occurred in the middle or outer part of the media without contact with the intima, an observation previously mentioned by *inter alia* Sproul and Hawthorne (1937).

Changes in the *intima* occurred less regularly than those in the media. A possibly specific change was a varying, lumen occupying, cushionlike thickening with loose tissue with metachromatic ground substance. This thickening of the intima has been described and discussed by Restrepo et al. (1969), who interpreted it partly as fibrosis, partly as proliferation of smooth muscle cells and an increase of the ground substance. In the present series it varied somewhat in appearance from one case to another. It could be seen adjacent to medial necroses, but also in arteries with a well preserved media (Fig. 14, 15). Hence, intimal lesions did not appear to be caused by, or to cause, medial injuries.

The *adventitia* sometimes showed diffuse fibrotic thickening of varying extent. Some dense groups of lymphocytes could be seen around the vasa vasorum, but often no inflammatory cells. The fibrosis might be a non-specific change, but it might also be a component of the picture of arteritis. No changes were seen in the vasa vasorum, which had thin, well preserved walls, and, in contrast with what has been suggested by some authors, *e. g.* Cooke et al. (1946) and discussed by *e. g.* Crosby and Wadsworth (1951) the arteritis did not appear to have been caused by injuries in the vasa vasorum. This theory was also denied by Kimmelstiel et al. (1957). In the cases with polyarteritis nodosa fibrinoid necroses were seen in the arterioles in the adventitia of the large arteries without necroses in the corresponding area of the arterial wall. This also argues against necroses of the media being caused by changes in the vasa vasorum.

Distribution of the changes

Lesions were found in the aorta in 12 of 15 cases in which it was examined. In six cases the entire aorta was involved, in one the proximal thoracic and distal abdominal aorta, in two the thoracic aorta, and in three the distal two thirds of the aorta. The aorta was thus involved in most cases but the extent of envolvement varied.

Changes were found in the arm arteries in 13 of 16 cases. Here, too, they varied in extent, the proximal parts being involved in 10, while in three the first parts of the subclavian artery were of normal microscopic appearance, distally thereto were found necroses in the media and in one case mural thrombi. — In 11 cases typical lesions were found in the carotid arteries. — In 10 cases there were more or less widespread changes in the leg arteries, consistent with earlier reports by *e. g.* Finlayson and Robinson (1955).

other authors. In a few cases there were thin reddish deposits on the aortic intima resembling those described by Gilmour (1941) and Frangenheim (1951). They did not look like ordinary thrombi. Mural, dark-red thrombi were found in the abdominal aorta in two cases, resembling the thrombi seen in some cases of pronounced atheromatosis. *In four of the cases the arm arteries showed changes*, which appear strange (though in vessel segments not examined routinely at necropsy) in the form of partial or complete narrowing between 10 and 20 cm from the origin of the subclavian artery from the aortic arch, in the proximal or distal part of the axillary artery. This is an interesting observation in agreement with the murmurs heard over the axillary arteries. No changes suggestive of arteritis were found in other large arteries.

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and calcification. Arteritis, which was more often found in the proximal part of the aorta had obviously not precipitated atheromatosis.

In one of the cases (V) with widespread ulcerations and calcifications, which could be interpreted as atheromatous, the histological picture was clearly that of arteritis with almost complete destruction of the media, that had been replaced by fibrous scar tissue. Varying amounts of round cells were found and scattered giant cells. Intimal fibrosis and calcification in this case, then, might have been secondary to arteritis. Arteritic changes were found also in better preserved arterial segments without atheromatous lesions. — In the young woman (XII) the macroscopical changes were not of atherosclerotic type but microscopically (Fig. 16) the intimal fibrosis with fat vacuoles was indistinguishable from atheromatosis. The medial lesions with total necrosis and clefts in necrotic elastic lamellae with penetrating capillaries were of clearly arteritic type. In this case, too, changes of atheromatous nature might be secondary to arteritis. Pronounced atheromatosis is otherwise not found in this age group.

In one of the cases (XIII), a woman of 76, the changes in the aorta were both macro- and microscopically of atheromatous nature. Medial necroses were found, but there was only mild round cell reaction, and they occurred in connection with intimal destructions. In this case, then, it was impossible to make a diagnosis of arteritis from the findings in the aorta. Atheromatosis might have existed before the development of the arteritis as the woman had been a heavy smoker for many years, a fact which is thought to aggravate atheromatosis, at least in some persons. I[n] the case with the most pronounced macroscopical changes (XIV) aorta unfortunately had not been examined microscopically. Atheromatotic changes were found also in the other cases which sometimes m[a]de it difficult to decide microscopically whether arteritic lesions existed or not. In most cases, however the medial necroses were clearly not of atherosclerotic nature.

Another degenerative process, involving mainly the aorta, is the so-called *Erdheim idiopathic cystic medial [n]ecrosis*. It seems to be of metabolic nature with alterations of the ground substance of the media. No changes are seen macroscopically unless rupture and dissection have occurred in the media. Microscopically irregular defects with separation of otherwise preserved elastic lamellae are seen. There are usually no inflammatory cells and differentiation of this medial necrosis from arteritis should offer no difficulties.

Syphilis has been regarded as a classical cause of arteritis. Such arteritis might be of different type, but affecting mainly the proximal part of the aorta with the aortic valves with dilatation and valvular insufficiency. The macroscopical changes are described as intimal thickening with coarse wrinkling and loss of elasticity of the artery wall. Microscopically obliterative endarteritis of the vasa vasorum with fibrous thickening of the adventitia and secondary destructions of the media with fibrous scars is said to be a predominant lesion. — All patients in the present material were tested with Wasserman's or Meinicke's reactions, and none proved positive. There were no other syphilitic manifestations in the cases and the macro- and microscopical pictures of the arteries seem clearly different from syphilis. However, cases of arteritis of the large arteries may earlier have been misdiagnosed as syphilitic arteritis.

Affection of arteries may occur in *rheumatic fever*, a systemic disease, affecting mainly the myocardium and the endocardium, and also appearing in chronic stages with fibrosis and granulomas. No signs of rheumatic carditis were found in the cases, and the lesions in the arteries were not of granulomatous type. A *rheumatoid arteritis* has been described, which occurs in patients with chronic rheumatoid arthritis and especially in chronic spondylitis. Arterial and other vascular lesions were surveyed by Klinge in Der Rheumatismus. The vascular changes varied, with an acute stage with *general oedema of the artery wall and diffuse in*filtration of lymphocytes and polymorphonuclears. In more chronic alterations fibrous scars were found in all layers of the artery wall and sometimes granulomas occurred. Similar lesions were found in the aortic valves and in the myocardium. — Widespread lesions in the myocardium, aortic valves and aorta were described by Clark et al. (1957), and by Heggtveit et al. (1963) in patients with chronic rheumatoid arthritis and spondylitis. The lesions were found mainly in the proximal part of the aorta, as in syphilitic aortitis and the microscopical changes also resembled syphilis with engagement of adventitia with obliterative endarteritis in vasa vasorum and general fibrosis, destructions in the media with fibrotic scarring

and with diffuse intimitis. Rheumatoid diseases are not well defined entities and the nature of the lesions is unknown. The arteritis in the present cases, however does not seem to fit in with these descriptions of rheumatic and rheumatoid arteritis.

Buerger's disease or thromboangiitis obliterans is also of unknown origin. It affects mainly men, it usually appears before the age of 35 years and is closely correlated with tobacco smoking. The morphologic changes are thrombosis of medium and small arteries and veins, inflammatory destruction of the thrombus and supposedly secondary changes in the artery wall, mainly with fibrosis. The intimal cushions, most pronounced in cases XII and XIII might have been organised thrombi and then be related to Buerger's disease. But the inflammatory changes in these cases were mild and there were no inflammatory changes around the arteries or in the veins. A common mechanism can not be excluded, especially as the older woman (case XIII) was known to have been a heavy cigarette smoker. Nothing was known about the young woman (case XII) in this respect.

Aetiology

The aetiology of polymyalgia and arteritis is unknown. The possibility of some immunological disorder has been suggested, with development of antibodies against the elastic substance of the arterial media, where the changes are most pronounced. Hamilton et al. (1971) and several others have, however pointed out that no changes are seen elsewhere in elastic tissues except in the arteries, and then the changes are not generalised. No changes that could be related to arteritis were found in the organs studied in the present analysis, and the injuries were found only patchwise in the large arteries. Attempts by Strachan et al. (1966) to demonstrate antibodies against elastic tissue have proved unsuccessfull. On the other hand, Waaler and Mikle (1968) demonstrated the occurrence of rheumatoid factor in biopsy specimens of the temporal artery of patients with polymyalgia rheumatica. — On examination of a large series of Takayasu-arteritis in Europe Ask Upmark and Fajers (1956) pointed out that the changes in the aortic arch may be of rheumatic or rheumatoid nature and that their localisation might be due to the hydrodynamic stress prevailing in the proximal aorta. Changes in Takayasu-arteritis appear more pronounced in the aortic arch and its large branches, but also several reports of similar diffuse or focal lesions distally in the aorta are available. Also the so called giant cell arteritis or temporal arteritis was formerly believed (Kilbourne & Wolff 1946) to be most common in the upper half of the body especially in the head, but several investigations (Gilmour 1941 Heptinstall et al. 1954 Finlayson & Robinson 1955) have revealed disseminated arteritis also in other arteries. Widespread arteritis was also found in the present series. It is therefore questionable whether local factors in the aortic arch play any role in the aetiology of the arteritis. — The inflammatory changes do not seem to be of rheumatoid type, there were no granulomatous changes, the necroses were not of fibrinoid type, and there was no engagement of the myocardium or endocardium. — The aorta and large arteries are not only conduits but can react to unknown stimuli with disseminated or localised changes as a result.

SUMMARY

During clinical follow-up of a material of polymyalgia arteritica 8 of the deceased patients were submitted to a systematic study of the large arteries. Four cases with the clinical diagnosis of temporal arteritis and two cases with no clinical history but gross findings at necropsy which suggested aortitis were studied in the same way. — The interval between the onset of symptoms and death was 1 to 15 years. — The patients were 65 to 88 years old at death, except one woman of 17 who had got the diagnosis of Takayasu's disease. — Two cases of polyarteritis nodosa, 56 and 67 years old and with symptoms of the disease for 2 and 3 months, respectively were examined in the same way.

The arteries were studied microscopically in transverse sections 2—3 cm apart from the aortic root to the base of the skull and the level of the elbow and the knee, respectively. About 100 sections were examined per case.

All the cases except the last two had widespread changes in the large arteries. They were most common in the aorta, both in the thoracic and abdominal aorta, but were seen to a varying extent in the large arteries of the upper and lower limbs. The lesions were patchy not coalescent and they often involved only part of the circumference of the artery.

Macroscopically the intima was thickened, wrinkled and had a pearly appearance, and the arteries were partly wider than normal

Microscopic examination showed irregular necroses in the media with dissolution of the elastic lamellae and destruction of the smooth muscle nuclei. Ingrowing capillaries, surrounded by numerous lymphocytes and plasma cells were seen around fragmented necrotic parts of the media. Varying numbers of multinucleated giant cells were found The necroses appeared to involve mainly the outer part of the medial layer The intima was thickened and the thickening did not appear to be secondary to the medial changes or to have caused them Intimal lesions consisted of loose tissue with smooth muscle and fibrous tissue nuclei and metachromatic ground substance. These intimal thickenings projected in a cushion-like fashion into the artery lumen. Deposits of fibrin could be seen and the intimal lesions might be organised thrombi No inflammatory reaction occurred around these intimal thickenings.

Adventitial fibrosis was seen in most cases, but it was mild and appeared to be secondary to the medial changes. The vasa vasorum were not changed The lesions seemed to be of varying age with active necrosis and inflammation occurring besides healing with fibrosis in one and the same case, suggesting that the arteritis is a chronic and migrating disease The young woman with Takayasu's disease had changes, largely resembling those of polymyalgia arteritica-patients, which suggests that the arteritis may be of the same type It appears to differ from syphilitic arteritis and the arteritic changes described in rheumatic and rheumatoid disease Arteriosclerosis of the vessels made it difficult to evaluate the arteritic changes.

The patients with polyarteritis nodosa had changes in the small arteries with a more acute inflammation and offered no differential diagnostic difficulties. The vasa vasorum of the large arteries were engaged but no lesions were found in the wall of the larger arteries. The investigation did not warrant any conclusions concerning the aetiology of the arteritic changes.

REFERENCES

Aggeler P M Lucia S P & Thompson, J H., Amer Heart J 22 825 1941

Ainsworth R W Gresham G A. & Balmforth, G V J Clin Path 14 115 1961

Alestig, K. & Barr J Lancet i 1228 1963

Allen, E V., Barker N W & Hines, E. A., Jr Peripheral Vascular Diseases (W B Saunders Company Philadelphia and London) 1962.

Allen, N & Mustian, V Medicine 41 227 1962.

Alonso T Angiologia 14 132, 1962.

Amsterdam, B & Amsterdam, A. L., New York J Med 43 2294 1943

Andersen T Acta Med Scand 128 151 1947

Andersen, T Acta Med Scand 128 230 1947

Andrews, F M Ann Rheum Dis 24 43., 1965

Andrews, J M Neurology 16 963 1966

Ansell, B & Byw ters, E G L., Brit Med J i 372, 1958.

Askey J M Amer Heart J 22 1 1941

Ask Upmark, E., Nord Med 21 434 1944

Ask-Upmark, E., Acta Med Scand 149 161 1954

Ask Upmark E. & Fajers, C. M Acta Med Scand 155 275 1956.

Bagratuni, L., Ann Rheum Dis 12 98 1953

Bagratuni, L., Lancet ii 694 1956.

Bagratuni, L. Ann Rheum Dis 16 104 1957

Bagratuni, L., Brit Med J i 513 1963

Bain, C. W C., Lancet i 517 1938

Baker J D Del Banco T L., Price J B Rogers, W M Salomon, P F & McAllister F F Surgery 59 88 1966

Balmforth G V Arch Intern Med 113 122, 1964

Barber H S Ann Rheum Dis 16 230 1957

Barker N W & Ed ds, J E., Circulation 11 486, 1955

Barnard, W G J Path Bact 40 433 1935

Barré J A., Rev Neurol 33 248, 1926.

Baumann, J M Z Klin M ed 158 22, 1964

Belfrage, S Acta Med Scand 173 Suppl 395 1963

Berg, K. & Lange H F Nord Med 69 333 1963

Bernmeier A & Held, K Z Kreislaufforsch 59 97 1970.

B rke, G Ejrup, B & Olhagen, B Angiology 8 433 1957

Birke, G & Ekelund, L -G Nord Med 6.. 1120 1959

Birkhead, N C., Wagener H P & Shick, R. M JAMA 163 821 1957

Björkman, S. E., Lancet 935 1958

Blorstad, Ö T Norsk Laegeforen 85 461 1965

Bowers, J M Arch Intern Med 66 384 1940

Boyle, A. C. & Beatty D C., Proc Roy Soc Med 54 681 1961

Brearley B F & MacDonald J G Brit Med J i 1151 1961

Brown, H Sellwood R. A Harrison C. V & Martin, P Brit J surg 56 59 1969

Bruce W Brit Med J ii 811 1888

Bruk, M I Ann Rheum Dis 26 103 1967

Bruns, D L. Amer J Med 27 360 1959

Bühler F Da Silva, A. & Widmer L. K., Schweiz Med Wschr 98 1932, 1968

B rstein, J Lindström, B & Wasastjerna C., Acta Med Scand 157 365 1957

Böttiger L. E., Acta M ed Scand 147 133 1953

Böttiger L. E., Acta Med Scand 156 469 1956—1957

Böttiger L. E., Blanck C. & Screeb, T von, Acta Med Scand 180 329 1966

Bottiger L. E. & Liljefors, L., Läkartidningen 62 2190 1965

Böttiger L. F & Molin L., Acta Med Scand 176 639 1964

Bött ger L. E. & Svedberg, C. A., Brit Med J ii 85 1967

Caceres, C A. & Perry L. W Editors, The I nocent Murmur A Problem in Clinical Practice (Little Brown and Company Boston), 1967

Cardell B S & Hanley T J Path Bact 63 587 1951

Carlander O S enska Läk Tidn 58 2109 1961

Cecil R. L. & Kammerer W H Amer J Med 10 439 1951

Codman, E. A., The Shoulder (The Author Boston), 1934

Committee Report, J p Heart J 9 76 1968

Cooke, W T Cloake, P C. P Govan, A. D T & Col beck J C., Quart J Med 15 47 1946.

Copeman W S. C., Lancet ii 1255 1961

Cremer H -D & Thelins, A., Biochem Z 320 273 1950.

Crevasse L. E. & Logue R. B., JAMA 167 2177 1958.

Crompton, M R., Brain 82 377 1959

Crosby R. C. & Wadsworth, R. C Arch Intern Med 81 463 1948

Cullen, J F Brit J Ophthal 51 513 1967

C rth, H. C., Amer J Med 1 437 1946.

Danaraj T J & Ong, W H Circulation 20 856, 1959

Damaraj, T J Wong, H. O & Thomas, M A., Brit Heart J 25 153 1963
DePalma, A. F Ann Surg 135 193 1952.
De Sèze, S., Fréneaux, B Bagros, Ph., Welfling, J Hubault, A., Kahn, M F Levérnieux, J Solnica J & Veber A., Rev Rhum 31 351 1964
De Sèze, S., Lequesne, M & Veber A., Sem Hop Paris 41 711 1965
De Sèze, S., Ryckewaert, A., Kahn, M F Mazabraud, A. & Lainée, R., Rev Rhum 28 563 1961
Dick, G F & Freeman, G JAMA 114 645 1940
Dickson, J A. & Crosby E. H JAMA 99 2252, 1932.
Dixon, A St. J Beardwell, C., Kay A W ka, J & Wong, Y T Ann Rheum Dis 25 203 1966
Dressler W Yurkofsky J & Starr M C., Amer Heart J 54 42, 1957
Duplay S., Arch gén Méd II 513 1872.
Duplay S., La Semaine Médicale 16 193 1896
Edling, N P G Nystrőm, B & Seldinger S. I Acta Radiol 55 417 1961
Edwards, E. A. & Levine, H D A M A Arch Intern Med 90 284, 1952.
Ernstene A. C. & Kinell, J Arch Intern Med 66 800, 1940
Finlayson, R. & Robinson, J O Brit Med J ll 1595 1955
Fisher M Arch Neurol Psychiat 65 346, 1951
Fisher M Arch Neurol Psychiat 72 187 1954
Fisher M Neurology 7 299 1957
Forestier J & Certonciny A Rev Rhum 20 854 1953
Forssman, C. O personal communication.
Frangenheim, H Zbl Allg Path 88 81 1951
Freyberg, R. H., Ann Rheum Dis 6 82, 1947
Frohnert, P P & Sheps, S. G Amer J Med 43 8, 1967
Frövig, A. G Acta Psychiat Neur Suppl 39 p 7 1946.
Frövig, A. G & Löken, A. C., Acta Psychiat Neur Scand 26 313 1951
Fuchs, G & Radloff H Arch Kreislaufforsch 37 134 1962.
Fåhraeus, R Acta Med Scand 55 1 1921
Gadrat & Moreau Arch Mal Coeur 45 830 1952
Garret, R., Amer J Clin Path 38 406, 1962
Garrison G E., Floyd, W L. & Orgain, E. S Ann Intern Med 66 587 1967
Garrod A. B Gout and Rheumatic Gout 3 ed, (Longmans, Green & Co London) p 496, 1876.
Garrod, A. E A Treatise on Rheumatism and Rheumatoid Arthritis (Charles Griffin and Company London), 1890.
Gelfand, M Brit Heart J 17 264 1955
Gierke, H E on, Medical physics O Glasser Editor (Th Yea Book Publishers, Chicago) 3 661 1960
Gillanders, L. A., Strachan, R. W & Blair D W Ann Rheum Dis 28 267 1969
Gilmour J R J Path Bact 53 263 1941
Gilroy J & Meyer J S., Circulation 25 300 1962
Gordon, I Quart J Med 29 473 1960.
Gordon I Rennie, A. M & Branwood, A. W Ann Rheum Dis 23 447 1964
Gotsman M S., Beck, W & Schrire V Radiology 88 232, 1967
Graham, W & Rosen, P B ll Rheum Dis 12 77 1962
Gydell, K. L., personal communication
Hamilton, C., Shelley W & Tum lty P Medicine 50 1 1971
Hammond, J H. & Eisinger R. P Arch I tern Med 109 563 1962.
Hamperl, H Virchows Arch 323 591 1953
Hamrin B Lakartidningen 63 3877 1966
Hamrin, B., Jonsson, N & Hellsten S Ann Rheum Dis 27 397 1968
Hamrin, B Jonsson, N & Landberg, T Lancet i 397 1964
Hamrin, B Jonsson, N & Landberg, T Lancet I 1193 1965
Hamrin, B & Thulesius, O Nord Med 84 1501 1970
H rris, M Brit Heart J 30 840 1968
Harrison, C. V J Clin Path 1 197 1948.
Harrison, M J G & Bevan, A. T Lancet ii 638 1967
H rrison R. J Harrison, C. V & Kopelman H Brit Med J ii 1593 1955
Hart, F D Brit Med J ii 99 1969
Harvey W De Motu Cordis. (Lugduni Batavorum, Ex fficina Ioannis Maire) 1639
Hedlund P Acta Med Scand Suppl 361 1961
Heggtveit, H. A., Hennigar G R. & Morrione, T G Amer J Path 42 151 1963
Henderson, A. H Brit Med J iv 337 1967
Hepthinstall, R. H., Porter K. A. & Barkley H J Path Bact 67 507 1954.
Hitch, J M Arch Derm 101 409 1970.
Hollander J L., Arthritis and Allied Conditions. J I Hollander Editor (Lea & Febiger Philadelphia) p 23 1969
Hollдack, K. & Wolf D Herzschall F bei Einführung in die Mechanokardiographie (Georg Thieme Verlag, Stuttgart), 1962.
Hollenhorst, R. W Brown, J R., W gene H P & Shick, R. M Neurology 10 490 1960
Holmgren L, Nord Med 16 3215 1942.
Holst, J E. & Johansen, E., Acta Med Scand 122 258, 1945
Horton, B. T Brit Med J I 105 1966.

Sproul E. E., New York J Med 42 345 1942.
Sproul E. E. & Hawthorne, J J Amer J Path 13 311 1937
Steinbrocker O Ann Rheum Dis 6 80 1947
Steinbrocker O Spitzer N & Friedman H H Ann Intern Med 29 22, 1948.
Steinbrocker O Arthritis and Allied Conditions, J L Hollander Editor (Lea & Febiger Philadelphia) p 1233 1969
Strachan, R. W Postgrad Med J 42 464 1966.
Strachan, R. W Wigzell, F W & Anderson, J R Amer J Med 40 560, 1966
Strandberg, O Acta Med Scand 180 Suppl 454 1966.
Sturm, A., Puentes, F & Scheja, H W Deutsch Med Wschr 95 1914 1970.
Takahashi, K., Arch Psychiat Nervenkr 111 373 1940
Talbott, J H & Ferrandis, R. M Collagen Diseases (Grune & Stratton, New York and London) 1956.
Thurlbeck W M & Currens, J H Circulation 19 499 1959
Todd J W Lancet ii 1111 1961
Ueda, H Morooka, S., Ito I Yamaguchi, H Takeda, T & Saito Y Jap Heart J 10 277 1969
Viero dt, H Daten und Tabellen für Medizin 3 Aufl (Verlag von Gusta Fischer Jena) 1906.
Vinijchaikul K., Amer J Med 43 15 1967
Waaler E. & Mikde, E. J Acta Path Microbiol Scand 72 347 1968.
Wadman, B & Werner I Lancet I 597 1967
Wagenvoort, C. A., Harris, L. E., Brown, A. L. & Veeneklaas, G M H., Pediatrics 32 861 1963
Waldenström, J Medicinsk Årsbok E Husted Editor (AB Nordiska Bokhandelns Förlag Stockholm) p 176, 1959—1960
Waldenström, J Harvey Lect 56 211 1961
Waldenström, J Monoclonal and Polyclonal Hypergammaglobulinemia (Cambridge University Press London), 1968
Waldenström, J Schweiz Med Wschr 100 2197 1970.
Waldenström, J A., Deutsche Klinik 26 172, 1874
W rrell D A Godfrey S. & Olsen E. G J Lancet i 1010 1968.
Warren R & Triedman L. J New Eng J Med 257 685 1957
Weissenbach R., Nobillot, A Freneaux, R. & Coste, F Sem Hop Paris 39 2073 1963
Westergren, A., Acta Med Scand 54 247 1921
Wickbom, I Acta Radiol 48 321 1957
Wiedermann, B Neoral, L. & Wiedermann, M Cardiologia 33 323 1958
Wilkinson, D S Textbook of Dermatology Vol 2 A Rook et al Editors (Blackwell Scientific Publications, Oxford and Edinburgh) p 1067 1968.
Wilske, K R. & Healey L. A Ann Intern Med 66 77 1967
Winblad, S Nord Med 32 2828 1946.
Wintrobe, M M Clinical Hematology (Lea & Febiger Philadelphia), 1967
Withers, R. J W J Bone Joint Surg 31B 414 1949
Zacharski L. R. & Kyle R A., JAMA 202 264 1967

Växjö 1971 C. Davidsons Boktryckeri AB

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PRIMARY AND CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Clinical and pathoanatomic observations

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INTRODUCTION

There are rather few sizeable materials of primary and chronic thromboembolic pulmonary hypertension reported in the literature (13 15 16 17 24 34 37 45 47) Additional documentation may be warranted, therefore Since occurrence classification and etiologic considerations of the disorders in question have been summarized elsewhere (39) the present communication is focused upon clinical aspects as they were met with in a catheterization material and as discussed in relation to some of the pertaining literature A brief account of pathoanatomic findings within the material also belongs to the purpose of the study

MATERIAL

From the third quarter of 1948 up to the fourth quarter of 1968 i e during a 20-year period 1268 patients have been subjected to right heart catheterization according to routine techniques not further described here at the Heart Laboratory of Malmö General Hospital. In 13 of them a diagnosis of primary or chronic thromboembolic pulmonary hypertension was entertained An additional patient (case no 14) was diagnosed in 1969 but is included in the series because of some interesting features

CASE HISTORIES

Basic patient data, and relevant symptoms and physical findings referring to the time of catheterization are summarized in table 1 Below are given short, supplementary histories of the patients in the order in which they were first heart catheterized. Most investigative findings relating to the pulmonary hypertension are not included in the case histories since they are represented separately in a tabular manner

Case 1 S L. ♂ born in 1944 He was well until 1949 when increasing exertional dyspnea insidiously started without preceeding illness or other associated symptoms In May 1950 pronouncedly accentuated pulmonary sound was noted. Standard lead electrocardiogram revealed accentuated and peaked P-waves in leads I-II and RS-quotient in lead I of 1 15/2 6 mV No treatment was instituted. His condition remained essentially unchanged with marked exertional dyspnea. He died suddenly in May 1955

Case 2 A.C ♂ born in 1924 Since childhood he had recurrent asthmalike dyspnea wheezing dry irritating cough, repeated upper air-way infections and sinusites Lip cyanosis was early noted In 1947 he was found to be allergic against a multitude of agents and marked cyanosis and clubbing of the fingers dyspnea and abundant expiratory and inspiratory sonore and sibilant rhonchi over both lung fields were noted. In 1953-1954 he had frequent loose stools Increasing exertional dyspnea and leg oedema developed. In 1954 he had an arterial oxygen saturation of 69 % slight eosinophilia and positive AST-titre Other serological tests were negative Skin eruptions and pruritus consistent with dermatitis herpetiformis were recorded. In spite of treatment with digitalis diuretics and steroids his further course was deteriorating In October 1956 he had severe CO_2-retention which necessitated respirator-care In September 1957 his condition again necessitated respirator-treatment, but he died in intractable right ventricular and respiratory failure in October 1957

Case 3 E G ♀ born in 1935 She is reported elsewhere (38) Reduced physical capacity was present already in 1945-1946 In 1948 exertional dyspnea insidiously developed. Menarche was at the age of 14. For a couple of years the dyspnea at effort

gradually progressed. Numerous syncopal attacks occurred. From the age of 16 years the symptoms successively improved. In 1955 she had moderate exertional dyspnea. Her condition remained satisfactory with persisting moderate exertional dyspnea but no syncopal attacks up to 1960-1961 when the exertional dyspnea slowly progressed and slight intermittent oedema, cardiac palpitations and occasional anginous chest pain at effort occurred From 1969 further deterioration has taken place with recurring sparse syncopal attacks and accentuated breathlessness fatigue chest pains cardiac palpitations and ankle oedema and also whitening and numbness of the fingers on cold exposure No lasting skin changes have occurred. Since 1960 she is kept upon a diuretic regimen, and since many years upon digitalis and anticoagulants In 1969 markedly increased thrombocyte-adhesivity was detected, and salicylates were instituted. She was re-investigated in November 1971

Case 4 S N ♂ born in 1916 In 1940 *positive Wasserman and Kahn reactions* were detected, but no clinical signs of syphilis and the TPI-test was negative. Between the years 1940-1944 he had repeated leg vein thromboses In 1941 suspect right-sided pulmonary embolus and bilateral crural ulcers developed. In November 1957 he had a bout of the Asian influenza After this he had increasing dyspnea at effort fatigue night sweatings and finally angionous chest pains I 1958 phlebograms revealed wide-spread occlusions in both leg veins and in the right brachial vein. Extensive serology was normal apart from persisting Wasserman and Kahn reactions He was treated with anticoagulants digitalis thiazides and from 1960 spironolactone but hi course was slowly deteri rating with fatigue dyspnea, oedema hepatomegaly venous congestion and pulsations anginous chest pains but *no syncopal attacks He died suddenly at* the 29th of March, 1962

Case 5 E.W ♀ born in 1947 She was always more tired than other children Her fatigue was somewhat further accentuated from 1957 In August 1958 she had a syncopal attack. She remained reasonably well without treatment until autumn, 1959 after which gradually increasing signs of right ventricular decompensation developed starting with exertional dyspnea. In spite of treatment with corticosteroids Priscol® anticoagulants digitalis and di retics deterioration was relentless with severe dyspnea, fluid retention massiv oedema hepatomegaly and venous congestion and pulsations Crural and decubital ulcers anginous chest pains frequent syncopal attacks peripheral circulatory failure with oliguria and mental confusion finally developed. She died after several days in a semicomatous state in January 1961

Case 6 G A. ♂ born in 1906 He was in excellent health until October 1959 when without preceeding illness dyspnea at effort started and gradually increased. In November 1959 retrosternal oppression occurred, and his exertional dyspnea limited him *to bed rest or sitting. In Februa*ry 1960 steroids and anticoagulants were instituted. His condition gradually worsened, with increasing dyspnea, anginous chest pains and slight intermittent ankle oedema. In 1961 a diastolic murmur in the third left costal interspace was heard. Digitalis was instituted. In October 1961 the liver was felt two fingerbreadths below the right costal margin, and a systolic murmur parasternally in the left fourth costal interspace appeared. There were no syncopal attacks He died suddenly in April 1962.

Case 7 S J ♀ born in 1918 She is reported elsewhere (28) In summary her symptoms insidously started already during puberty with light dyspnea at effort, reduced physical capacity and vertigo-like attacks but no faintings Some accentuation of the symptoms occurred after her *first childbirth in 1941* and syncopal attacks and cardiac palpitations occurred from 1942. She had a second complication-free childbirth in 1947 From 1950,

there has been intermittent ankle oedema Her exertional dyspnea has slowly increased while the syncopal attacks have waned. In the last few years slight chest oppression at effort and since three years whitening and numbness of the fingers and toes on cold exposure have appeared During the same time marked cutaneous depigmentations in the hands and feet have developed, but no certain skin atrophy or lasting ulcerations

Case 8 S G ♂ born in 1916 In 1959 without proceeding illness exertional dyspnea slowly developed and in August, 1960 markedly reduced physical capacity The patient denied other symptoms In February 1961 a steroid, theophylline and diuretic regimen was instituted. Increasing severe dyspnea fatigue oedema hepatomegaly and nausea developed He was admitted to his local hospital in March, 1962 12 hours after the admission, the blood pressure rapidly fell to a systolic level of 70 mm Hg the patient lapsed into a shock-like semi-comatous state and he died in spite of Aramine® infusion. Postmortem examination revealed pronounced right ventricular and atrial dilatation and hypertrophy no heart defects and in the pulmonary artery and its branches abundant atheromatous plaques but no macroscopic thromboemboli Microscopic investigation was not performed.

Case 9 H D ♀ born in 1898 She is reported in detail elsewhere (40) In 1946 she first noted dyspnea at effort and intermittent ankle oedema. Investigations have revealed a pulmonary arterial aneurysm, which has attained enourmous size and now occupies considerable space in both middle hemi-thoraces probably interfering with respiratory function. Her present symptoms apart from effort dyspnea, are occasional tachycardia chest oppression and moderate intermittent ankle oedema Electrocardiographical signs of left ventricular hypertrophy and strain have developed too No signs of conditions possibly relating to the pulmonary arterial aneurysm such as syphilis or Marfan s syndrome have been detected

Case 10 M S ♀ born in 1913 She underwent multiple surgical procedures between 1940-1945 In the beginning of the 1940 s she had a right-sided femoral vein thrombosis with an episode of acute right sided chest pains In July 1966 she fell ill with intermittent, left-sided chest pains nonproductive irritating cough diarrhoea fever perspiration and pronounced fatigue. She gradually and protractedly improved but tiredness weakness subfebrility and exertional dyspnea persisted In September 1966 ESR was 55 ml/l hour WBC 18 700/mm^3 and chest X-ray showed parenchymal changes within the left lingula In November 1966 these abnormalities had disappeared, but she complained of recurrent, sharp lower left thoracal pains Subsequently the symptoms improved upon an anticoagulant and diuretic regimen In 1968-1969 diffuse arthralgias occurred. Detailed laboratory investigations including extensive serology were largely unrevealing apart from persisting cytomegal virus titre 1/256 in September 1969 and November 1971 Cytomegalvirus isolation in 1971 was negative

Case 11 E A. ♂ born in 1913 In the 1950 s he had repeated iridocyclites and periods of tiredness and elevated ESR rate but no arthralgias genitourinary or other local symptoms Extensive serology lues serology and TPI-test are negative There are no external stigmata of Marfan s syndrome or of Ehlers-Danlos disease and repeated roentgenologic investigations of the vertebral column and sacroiliac joints have revealed no ankylosing spondylitis changes In the last few years dyspnea at effort has occurred. Routine chest X-ray in 1968 showed wide thoracic aorta with calcifications suggesting luetic aortitis and aneurysmatically dilated pulmonary arteries (fig 1a) Subsequently angiocardiographic investigation revealed a) pronounced, aneurysmatic dilatation of the entire thoracic aorta but no aortic valvular incompetence (fig 1c) b) aneurysmatic central pulmonary arteries which in the next generations were markedly wide and tortuous and had an anomalous







Fig 1 Roentgenologic findings in case 11
a. Frontal chest X ray Very wide aortic silhouette with calcifications (black arrow) wide pulmonary arterial segment, and aneurysmatic dilatation of the right main pulmonary artery and descending branch (white arrow)
b Pulmonary angiography Note aneurysmatic dilatation of the main pulmonary artery peripheral pulmonary arterial aneurysms (black arrows) wide and tortuous peripheral pulmonary arteries and abrupt blocking of peripheral pulmonary arteries (white arrow)
c Aortography Very wide thoracic aorta, but competent aortic valves

course and multiple aneurysm like dilatations (fig 1b) and c) abrupt and irregular narrowings of peripheral pulmonary arteries (fig 1b) There were no signs of intracardiac or intrapulmonary shunts Left heart catheterization in May 1968 revealed normal left ventricular (117/0-5 mm Hg) and aortic (117-129/47-65 mm Hg) pressures without signs of aortic valvular insufficiency Temporal and radial artery biopsies were normal as was phlebographic investigation Radiospirometry revealed markedly decreased perfusion of the left lung (29 % of the total perfusion) particularly in the lower parts

Case 12 L.G ♀ born in 1919 She has been reported elsewhere (26) This patient had consumed large amounts of appetite-suppressing drugs From December 1967 severe and rapidly progressive pulmonary hypertension developed in which she succumbed in the picture of right cardiac and sudden peripheral circulatory failure in August, 1969

Case 13 E P ♀ born in 1912 She is also previously reported (43) Since 1940 she had blanching and cyanosis of the fingers on exposure to cold, since 1960 small hard subcutaneous nodules at different locations of her body and since 1968 progressive effort dyspnea and anginous chest pains Investigation revealed systemic sclerosis and pronounced, fulminating pulmonary hypertension, in which she died in December 1969

Case 14 E R. ♀ born in 1903 In the spring of 1968 she fell ill in a "gastroenteritis with fever tiredness pronounced sweatings diarrhoeas myalgic neck pains and throbbing ache in the left eye The symptoms slowly subsided but the patient was left with fatigue exertional dyspnea and a feeling of "nervousness" and reduced physical capacity After an influenza like illness at Christmas time 1969 these discomforts markedly increased and intermittent ankle oedema cardiac palpitations and occasional chest oppression started. Digitalis was prescribed In September 1970 she was first admitted to the medical clinic in Malmö and moderate systemic hypertension and marked pulmonary hypertension were found. Her condition improved after diuretic treatment. The further course has been characterized by twice recurring periods of right ventricular failure with marked fluid retention dyspnea at rest and attacks of "vertigo" but no syncopes The relapses were largely due to failing adherence to given prescriptions reinstitution of which during subsequent hospitalizations promptly brought about marked improvement. At present she is satisfactory maintained upon a digitalis spironolactone furosemide and anticoagulant regimen. Her main persisting symptoms are dyspnea at effort intermittent ankle oedema and easy fatiguability Apart from hyperuricemia (maximal value 14 6 mg/100 ml) hyperglucosemia (maximal value 324 mg/100 ml) and glucosuria (maximal value 6 5 g/100 ml) possibly related to her medication a few other investigative findings besides those tabularly represented warrant consideration.

Consecutive laboratory values WBC 5 700-7 100-5 700 with N 45-53 5-59 % E 2-3-0 % B 1 5-0 5-0 % L 44 5-33-33 % and M 9-8-8 % Thrombocytes 74 000-120 000-147 000-202 000 Serum GOT and GPT normal-upper normal but serum LDH 625-885-640 units with elevation of iso-enzyme fractions 1 2 and 3 serum alkaline phosphatases 12-18 units serum GT 290-470-98 units serum haptoglobin 1 19 mg/100 ml IgM 0 42-0 23 g/100 ml IgG 0 8 g/100 ml and IgA 0 13-0 08 g/100 ml COHb Coomb s test and extensive serology negative Virus serology negative apart from positive cytomegalvirus titre 1/256 both in May and October 1971 Cytomegalvirus isolation has been negative however

Other investigations Left-sided fore-leg phlebography did not reveal post-thrombotic changes Temporal artery biopsy in February 1971 showed degenerative changes in the elastica and a vessel lumen partly obliterated by intimal proliferation but no inflammatory cell infiltration (fig 2)



Fig 2 Temporal artery biopsy in case 14 Re-duplication of the elastic membranes. Elastin x 74 Areas of lumen-narrowing intima proliferation were seen in other sections and might possibly be consistent with previous arteritis or thrombosi

FINDINGS

A. Clinical findings

Recorded symptoms and physical signs (table 1) and phonocardiographic (fig 3) electrocardiographic (fig 4) roentgenologic (table 2) spirometric (table 3) and heart catheterization findings (table 4) are tabularly summarized as are results in performed exercise tests (table 5 routine laboratory analyses (table 6) and, in 9 of the cases detailed coagulation investigations (table 7) The findings will be briefly commented upon in the discussion

B Pathoanatomic findings

They are represented in table 8 Figures 5-8 show some examples of patho-anatomi lesions of primary and chronic thromboembolic pulmonary hypertension met with in the autopsied cases within the material

It may be noted that case 1 exhibited recanalized thrombi in peripheral pulmonary arteries (fig 8c) However thrombotic occlusion of mall pulmonary arteries may sometimes occur in cases of primary pulmonary hypertension (44) He had no macroscopic thromboemboli In a few pulmonary arterial ramifications in case 1 changes suggestive of arteritis were seen (fig 8c) They may possibly be a non-specific expression of severe pul monary hypertension, particularly in infancy (see 29) Similar changes were not found in any of the other cases Hyperplastic lesions in peripheral pulmonary arteries were sparse in case 5 It is well-known that there may sometimes be a discrepancy between the linical severity and the subsequent microscopic findings in primary pulmonary hypertension although cases quite devoid of lesions in the small pulmonary arteries probably do not exist (44) The pathoanatomic findings in case 2 differ from the others in terms of the pulmonary parenchymatous

Case	Family history	History of previous thrombosis	Appetite-suppressing drugs	Sex	Month and year	Age (years)	Duration of symptoms (years)	Nervousness*	Effort dyspnea	Ortopnea dyspnea at rest	Cyanosis	Intermittent ankle edema	Stationary edema	Hepatomegaly	Anginous chest pains	Cardiac palpitations	Syncopal attacks	Acc 2nd pulmonic sound	Right ventricular lift	Jugular venous pulsations	Diastolic murmur	Systolic murmur	Raynaud syndrome	Finger clubbing	Systemic blood pressure (mm Hg)	Height (cm)	Weight (kg)
1	No	No	No	♂	0560	6	1	No		(+)	No	No	No	No	No		No	+			No	(+)	No	( )	125/75		15
2	No	No	No	♂	0554	30	25	No	+				+	+	( )	( )	No		+		No	No	No		105/80	175	65
3	No	No	No	♀	0555	20	10	( )	+	(+)	No	No	No	No	No	No	+	+	(+)		(+)		No	No	130/70	162	57
3	No	No	No	♀	1171	36	26		+	+	( )		No	No	+	+	+	+	+	+	+	+	No	(+)	105/80	163	49
4	No		No	♂	0358	42	1/2	No		(+)	(+)	(+)	No	+	+	No	No	+		+	No	No	No	No		176	60
4	No		No	♂	0361	45	3 1/2	No	+	+	+	+	+	+	+	+	No	+	+		No	+	No		115/75	176	80
5	No	No	No	♀	0459	12	>2	No	+	No	No	No	No	No	(+)	No	+	+			+	No	No	No	115/65	147	30
5	No	No	No	♀	0260	13	>3	No		+	(+)	+	No	No	(+)	No		+			+	+	No	No	105/60	153	35
6	No	No	No	♂	1259	53	1/6	No	+	(+)		No	No	+	( )	No	No	+		+	+	No	No	No	110/90	161	73
7	No	No	No	♀	0460	44	>25	No	+	No	No	No	No	No	No	+	+	+		No	No		No	No	115/75	207	70
7	No	No	No	♀	1171	55	>36	( )	+	(+)	(+)		No	No	(+)	+	No	+	+	(+)	No	(+)	No*	No	120/80	166	70
8	No	No	No	♂	0161	45	1 1/2	No		( )	+	No	No	No	No	No	No	+		-		( )	No	No	115/90	177	76
9	No	No	No	♀	0661	63	>15	No	+	No	No	( )	(+)	No	No	No	No	( )		-	(+)	+	No	No	150/105	168	76
9	No	No	No	♀	1171	73	>25	No	+	(+)	(+)	+	(+)	No	No	( )	No	+	+	No	+	+	No	No	140/100	163	65
10	No	+	No	♀	0167	54	1/2	(+)	+	No	No	No	No	No	No	(+)	No	(+)	No	No	No	No	No	No	110/70	164	45
11	?	No	No	♂	0568	55	a few**	No	+	No	No	No	No	No	(+)	No	No	+	No	No	No	+	No	No	150/80	185	76
12	No	No	+	♀	0868	51	3/4	+	+	(+)	(+)	+	No	No	(+)		+	+			No	(+)	No	No	150/105	155	62
12	No	No	+	♀	0269	52	1 1/4	+		+	+	+	(+)	+	+	+	+	+	+	(+)	No	+	No*	No	145/105	155	63
13	No	No	No	♀	0969	58	3/4	No	+	+	+	+	+	+	+	+	+	+	+	+	No	(+)	+	( )	115/85	157	60
14	No	No	No	♀	0970	63	2 1/2	(+)	+	(+)	+	+	No	No	(+)	( )	No	+	+	(+)	No	No	No	No	150-220 / 105-120	161	74
14	No	No	No	♀	1071	64	3 1/2	(+)	+	(+)	+	+	(+)	No	(+)	+	No	+	+	(+)	No	No	No	No	105/110	161	62

information lacking   whitening and numbness of peripheral extremities on cold exposure   + yes

Table 1: Anamnestic data, symptoms and signs in the material

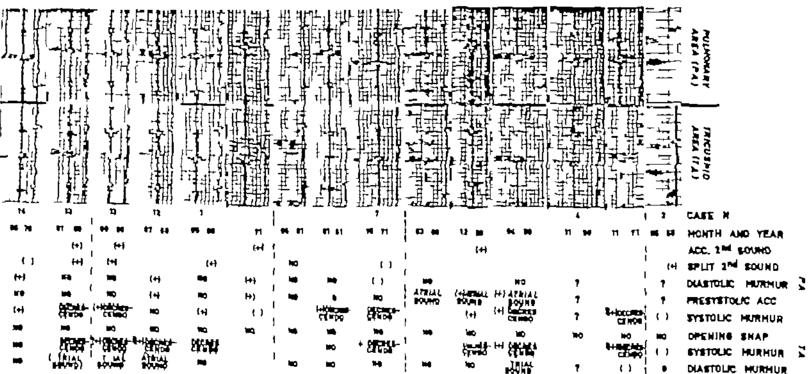


Fig 3 Phonocardiographic findings within the material Medium to high-frequency recording and in some of the cases also recording of the whole frequency spectrum are represented Broad accentuated and split second heart sound over the pulmonary area was a regular finding Systolic murmurs usually of decrescendo-type with P M. over the tricuspid area and slight diastolic murmurs of decrescendo-pandiastolic type with P M. over the pulmonary area were recorded in many cases

I II III VR VL VF V1 V2 V3 V4 V5 V7 (V1) (V2) (V4) (V5) (V7) 1mV

Case nr	2		3		6	5	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	10			13	14
Month and year	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Heart rhythm	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus	Sinus
Heart rate	92	87	75	55	76	66	125	72	66	90	90	69	83	60	66	90	93	95
P-Q-time (seconds)	0.12	0.2	0.21	0.19	0.14	0.205	0.13	0.17	0.15	0.175	0.165	0.155	0.16	0.14	0.16	0.16	0.16	0.2
IV block?	No	No	Total RBB	No	No	Total RBB	H	No	No	No	No	No	No	No	I.R.B.B.	Total RBB	No	No
Frontal P-wave axis	55°	35°	75°	65	75	55	75	75	60°	75°	65	60°	60°	75	80°	65°	25°	+60°
Frontal T-wave axis	55	10°	-45	16	75	70°	25	25°	+40°	+40°	+45°	30°	?	+60°	40°	10°	60°	20°
Frontal QRS-axis	120°	120°	160°	100°	85	110	120°	120°	100°	95°	120°	90°	85	85°	60°	135	130°	140°
Angle QRS-T	165	120°	205°	85	60°	100	145	145	60	50°	75	30	?	20°	20°	145°	100°	100°
Pulmonary P-waves?	++	( )		0	0		0	( )	0	0		0	0	0	0		(+)	
RV hypertrophy V1	( )	++	++		0	++		++		(+)	(+)	(+)	?	?	?	++	(+)	++
— — V5	++	(+)	++		0	(+)	++	( )	0	(+)?		0	0	0		++	++	++
RV strain?	++	0		++	++	++	(+)				( )	++			( )		(+)	
LV — —?	( )	0	( )	( )	(+)		0	(+)	( )	(+)	0	(+)		0	0	0	( )	0

Fig 4 (Abbreviations IRBB = incomplete right bundle (branch) block, IV = intraventricular LV = left ventricular RV = right ventricular)

Electrocardiographic findings within the material The findings are tabularly represented below the electrocardiographic recordings Criteria of right ventricular hypertrophy largely accord to the Minnesota Code although a few additional criteria were applied as well

Case nr	Chest X ray (month and year)	Angiocardiography (month and year)	Heart volume (ml)	Heart volume/m² B.S.A. (ml)	Right ventricular enlargement	Right ventricular hypertrophy	Right atrial enlargement	Left ventricular enlargement	Wide central pulmonary arteries	Scanty peripheral pulmonary arteries	Slow contrast passage	Pulmonary parenchymatous changes	Signs of pulmonary stasis
1	0550	No	305	460	+	–	(+)	+	+	–	–	No	No
2	0554	No	2475	1440	+	–	–	+	–	+	–	+	No
3	0555	0555	570	380	(+)	No	No	No	+	+	+	No	No
3	1171	No	900	600	+	–	+	(+)	+	+	–	No	No
4	0158	No	1600	775	+	–	+	(+)	+	–	–	No	No
4	1261	No	–	1000	+	–	+	+	+			No	No
5	0660	0459	–	–	+	+	(+)	(+)	+	+	+	No	No
6	1259	1259	1220	590	+	(+)		No	+	+	+	No	No
7	0460	0460	750	420	+	+	(+)	No	+	+	+	No	No
7	1171	No	1020	560	+	–	(+)	(+)	+	+	–	No	No
8	0161	No	1700	890	+	–	(+)	(+)	+	+	–	No	No
9	0661	0661		–	+	+	+	No	++	+	+	No	No
9	1171	No	–		+	–	+	(+)	+++	+	–	No	No
10	0167	No	710	450	No	–	No	No	No	–	–	No	No
11	0568	0568	1000	540	(+)	–		(+)	+	+	+	No	No
12	0868	0868	1120	700	+	+	(+)	No	+	+	+	No	No
13	0968	0968	960	610	+	+	+	(+)	+	+	+	No	No
14	0970	0970	1060	600	+	+	+	(+)	+	+	+	No	No
14	–	1071	–		+	+	+	(+)	+	+	+	No	No

(= investigation not performed or sufficient information lacking)
(+ = yes)

Table 2: Roentgenologic findings in the material

Case nr	Month and year	VC (% of calculated normal value)	TLC (% of calculated normal value)	FRC (% of calculated normal value)	RV (% of calculated normal value)	FRC/TLC (%)	RV/TLC (%)	MVV_F (% of calculated normal value)	$FEV_{1.0}$ (% of calculated normal value)	N_2-time (minutes)	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)
2	0857	90	81	89	161	67	59	12	19	7	62	60
3	0555	82	86	91	103	52	26	99	-	2 3	-	-
3	1171	65	87	79	92	49	27	86	91	3		
4	1258	75	83	79	108	49	25	39	69	2	-	-
6	0160	74	70	71	64	60	29	60	64	2 6	62	25
8	0161	87	90	104	94	61	29	53	-	1 8	60	26
8	0661	98	73	-	-	54	27	114	70	2 8	86	35
9	1171	49	61	75	82	62	48	39	50	3 8	6[illegible]	43
10	1266	92	122	129	189	61	47	80	104	4 3	73	37
10	0268	108	123	129	165	58	39	99	106	2.3	76	42
11	0666	64	89	85	101	50	34	69	89	2 5	65	33
12	0568	69	110	142	162	56	41	69	85	1 8	61	31
13	0968	60	109	154	175	67	48	64	81	1 3	71	32
14	0970	103	122	162	158	55	44	97	118	2 9	75	36

- = information lacking

Table 3: Lung function values in the material

Case nr	Month and year	Right atrium a"	Right atrium v"	Right atrium m̄	Right ventricle s	Right ventricle id	Right ventricle ed	Pulmonary artery s	Pulmonary artery d	Pulmonary artery m̄	PCV m̄	Cardiac output (l/min)	PVR index (units)	Signs of intra-cardiac shunts
		Pressures (mm Hg)												
1	0550	6	1	3	125	2	11	118	58	-	-	-	-	No
2	0554	10	5	6	75	2	11	85	37	49	16	7.6	4.4	No
3	0656	6.5	4	2	49	0	0	46	12	28	8	-		No
3	1171	13	6.5	7	77	5	11	79	37	49	11	-	-	No
4	0358	6	4.5	3	56	0	1	-				-		No
5	0459	4	4.5	3	67	1	7	63	27	44	5	2.8	13.5	No
5	0260	10.5	6	5	89	0	10	87	39	51	-	2.3	-	No
6	1259	6	5	4	95	-3	9	91	30	54	-		-	No
7	0460	12.5	10	9	58	6	7	57	26	38	-	2.7	-	No
8	0161	7	2.5	3	74	0	3	77	33	50	5	2.4	18.5	No
9	0661	14	8	7	60	1	7	50	25	33		4.6	-	No
9	1171	7	3	1	52	2	7	48	26	34	-	-		No
10	0267			3	33	0	1	33	8	20	5	4.7	3.1	No
10	0468	-	-	3		-		12	6	9	3	4.5	1.3	No
11	0568	6	4	4	45	0	3	46	15	30	-	6.6	-	No
12	0668			5	92	3	10	95	38	56	2	3.2	17	No
13	0259	-		14	98	4	13	97	47	65	16	2.8	18	No
13	0968	6	4.5	4	66	3	10	78	32	60	3	2.5	19	No
14	0970	9	3	3	93	0	5	97	33	62	-		-	No
14	1071	10	4.5	5	92	1	5	85	34	50	8	4.4	9.1	No

Abbreviations
"a" = a wave
"v" = v wave
s = systolic
d = diastolic
id = initial diastolic
ed = end-diastolic
m̄ = mean

PCV = pulmonary capillary venous
PVR = pulmonary vascular resistance

Table 4: Heart catheterization findings in the material

Case nr	Month and year	Platelet adhesivity (%) **	Cryoglobulin	Cryofibrinogen	Fibrinolytic split products	Other pathologic findings?
3	1171	29*	No	(+)	No	No Venous vessel wall plasminogen activators normal
4	0458	-	-	-	-	Markedly increased prothrombine consumption.
						Markedly increased urokinase inhibition.
7	0172	28	No	No	No	Fibrinogen 0 51 g/100 ml Otherwise normal findings
10	0567	29–	No	No	No	Markedly decreased fibrinolytic activity after venous stasis
	1171	34				Markedly decreased venous vessel wall plasminogen activators
		20				Fibrinogen 0 43 – 0 30 g/100 ml.
11	0668	-		-	-	No
12	0868	57	No	No	No	Slightly increased urokinase inhibition.
13	0968	46	No	No	-	Slightly increased urokinase inhibition.
						Decreased fibrinolytic activity after venous stasis
14	0670–	19–	No	No	+ (0271)	Slightly increased urokinase inhibition.
	0571	29				Markedly decreased fibrinolytic activity after venous stasis
						Decreased venous vessel wall plasminogen activators

(- information lacking)
* During salicylate treatment
** Normal value of platelet adhesivity = 17–33 %.

Table 7: Coagulation analyses in the material

Case nr	Autopsy nr	Heart weight (g)	Thickness of right ventricular wall	[illegible]	Pulmonary rteries		Associated conditions
					Macroscopically	Microscopically	
1	[illegible]	[illegible]		Fenestrations up to 4–5 mm	Marked rteriosclerosis No macroscopic thrombi.	Moderate hyperplasi of intima and media In many small rteries organized and recanalized thrombi. Slight rteritis?	Pulmonary emphysema (slight, bullous) (Slight subvalvula pulmonary stenosis?)
3	[illegible]/57	[illegible]	10 mm	Closed	Marked arteriosclerosis Many wall-adherent thrombi in the right main branch	Multiple rganized and recanalized thrombi in rteries of varying sizes (Many infarctions)	Bronchi l asthma. Chronic bronchitis Bronchiectasis. Pulmonary fibrosi (slight) Fibrosing alveolitis Thrombi in right jugular and subclavian veins
4	[illegible]	[illegible]	[illegible] mm	Closed	Marked rteriosclerosis Wall-adherent thrombi in many branches large wall-adherent thrombi in the right pulmonary tery	Multiple organized and recanalized thrombi in both large and small branches	Thrombi in femoral and iliacal veins bilaterally
5	[illegible]	[illegible]	[illegible] mm	Closed	Marked arteriosclerosis	Moderate rteriosclerosis in large and medium-sized branches. Moderate hyperplasi of medi and intima.	Slight emphysema
[illegible]	[illegible]	[illegible]	[illegible] mm	Closed	Marked rteriosclerosi Multipl emboli	Multiple rganized and recanalized thrombi	
11	[illegible]	[illegible]	10 mm	Closed	Prominent rteriosclerosis	Marked hyperplasia of intima of the small rteries Muscular hyperplasia partly with hyalinization	
12	113/[illegible]	[illegible]	[illegible] mm	Closed	V ry marked rteriosclerosis	V ry marked hyperplasia of intima and media in small and medium-sized rteries	Systemic sclerosis

Pronounced hypertrophy"

Table [illegible] Pathoanatomical findings in the material.





Fig 5 Pathoanatomic findings in the material a. The lungs and heart of case 5 Pronounced predominantly right-sided cardiomegaly

b Case 12 Pronounced right ventricular hypertrophy

b Case 4 Pronounced right ventricular hypertrophy





Fig 6 Macroscopic appearance of the large pulmonary arteries in primary and chronic thromboembolic pulmonary hypertension. a. Primary pulmonary hypertension Case 5 No macroscopic thromboemboli abundant fibrous atherosclerotic plaques b Chronic thromboembolic pulmonary hypertension Case in the autopsy study of chronic pulmonary thromboembolism Massive occlusion of the main pulmonary arteries by old, organized, partly wall-adherent thrombo-emboli extending into smaller pulmonary arterial branches



a



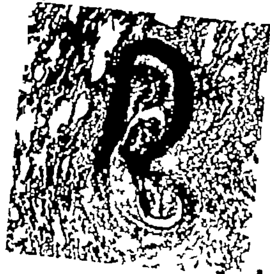
c



b

Fig 7 a. Case 12 Hilar region of section of right lung prepared according to Gough. The arteries show marked atherosclerosis with *thickened walls* but there are no thromboemboli in their lumina
b Case 6 Organized and recanalized thrombus in a medium-sized pulmonary artery H-E x 26
c Microscopic appearance of the pulmonary parenchyma in case 2. Upper part. *Inflammatory changes* in a bronchial wall Lower part: Slight fibrosis of the alveolar septa, abundant alveolar macrophages Picture consistent with fibrosing alveolitis H E x 64.

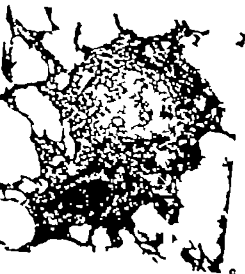
Fig 8


a




b


e


c


f

Fig 8 Microscopic findings in primary and chronic thromboembolic pulmonary hypertension.
a (Case 4 H E x 35) – b (Case 6 Elastin x 25) show findings in the latter group with organized and recanalized thrombi mainly in medium-sized and small pulmonary arteries c – f, show findings in the primary pulmonary hypertension group c Case 1 Two small pulmonary arteries The upper one exhibits moderate thickening of the media and is occluded by a recanalized thrombus The lower one exhibits arteritis-like round-cell infiltration of the wall and the occluded lumen. H-E x 89 d. Case 5 In the upper part an arteriole with irregular intimal proliferation is seen. In the lower part there is a pre-arteriolar pulmonary arterial branch with pronounced lumen-narrowing media and intima hyperplasia H-E x 156 e Case 12 Small pulmonary artery with pronounced cellular intima hyperplasia of "onion-skin" type H E x 85 f. Case 13 Two small pulmonary arteries with reduplication of the elasti membranes and very pronounced cellular intima proliferation. In the upper artery the cellular intima hyperplasia seems to encircle three separate very narrow vessel lumina within one common media coat. This type of lesion is not uncommon in primary pulmonary hypertension and is usually designated angiomatoid lesion *Elastin x 127*

lesions (fig 7) Also from a clinical point of view he would seem to belong to the group of pulmonary hypertension in pulmonary parenchymatous disease rather than to chronic thromboembolic pulmonary hypertension. He is included here however since pronounced chronic pulmonary thromboembolization was present as well Cases 4 and 6 and cases 12 and 13 demonstrate typical lesions of chronic thromboembolic pulmonary hypertension and primary pulmonary hypertension respectively (fig 7a–b 8a–b e–f) They also demonstrate that clear-cut differences usually exist in the pathoanatomic picture between these two conditions (see 44)

DISCUSSION

I Represented disorders

Even after restricting primary pulmonary hypertension to pulmonary arterial pressure-increase in intrinsic disorders of the pulmonary arterial vessel wall (9) it is a very heterogenous disease group (39) Similarly chronic thromboembolic pulmonary hypertension embraces a multitude of possible causations and may exhibit different modes of onset and progression (39) The above considerations are reflected in the present material by the inclusion of two cases of pulmonary arterial aneurysm, in which moderate pulmonary hypertension was present and as far as could be ascertained was connected but with the special type of pulmonary arterial vessel wall affection in question Both cases are unusual. Case 9 is the first reported follow-up-catheterized case and exhibited several interesting features plausibly relating to the course of her disorder at the re-investigation (see 40) Case 11 represents a combination, to our knowledge not hitherto recorded, of aneurysmatic *widening of the thoracic aorta* and multiple aneurysmatic and stenotic abnormalities of the pulmonary arteries Combination of supravalvular aortic stenosis with peripheral coarctations of the pulmonary arteries (5 27 39) and of peripheral coarctations of the pulmonary arteries with tortuosity of pulmonary and systemic arteries (25 37) are known. Marfan s syndrome may be associated with pulmonary arterial (28 40) as well as with aortic aneurysms (28) although the actual co-exis-

tence of them in the disorder is not well-documented This is true for syphilis too (39 40) There is no evidence of Marfan s syndrome or of syphilis in case 11 Repeated iridocyclites are suggestive of Bechterew s disease but manifest ankylosing spondylitis or aortic insufficiency have not developed Similarly there are no firm indications of previous endocarditis in which speculatively both aortic (32) and peripheral pulmonary aneurysms (39) might develop Peripheral pulmonary aneurysms have been recorded in some other inflammatory conditions as well (20 39 40) and may remind in angiographic appearance of the present case (20) However several reported cases of presumably congenital "tortuosity" (4 27) "weeping willow pattern" (8) "multiple large branch stenoses" (8 35) and other abnormalities (23) of the lung arteries also remind in pulmonary arterial pattern of case E A. Possibly both his aortic and pulmonary arterial abnormalities might have a common embryonal denominator considering the origin of the VIth aortic arches from the aortic truncus (see 42) Relation to previous inflammatory disease cannot be excluded however and there is also the possibility that the aortic and the pulmonary arterial lesions are independent of each other

Also included in the material is a patient with fibrosing alveolitis and wide-spread pulmonary arterial thrombose-formation (case 2) since pulmonary parenchymatous diseases have been repeatedly reported to be associated with this complication and thus constitute one of the many possible causations of chronic pulmonary thromboembolism (39) His pulmonary hypertension was probably more correlated to his pulmonary dysfunction (42) than to the pulmonary artery thromboses however

The other 11 cases are heterogenous too 6 of them may be classified as primary pulmonary hypertension (cases 1 3 5 7 12 13) One of them exemplifies suspected drug-induced pulmonary hypertension (case 12) (26) and one a clear-cut collagenosis variety of primary pulmonary hypertension (case 13) (43) The other 4 may be termed "idiopathic pulmonary hypertension" (39) In case 7 however there were some features known to occur in auto-immune states such as vitiligo (see 38)

Cases (2) 4 6 and 10 represent chronic thromboembolic pulmonary hypertension. There was a history of previous thromboemboli in two of them (4 and 10) but not in case 6 The series is clearly small but may still reflect some of the clinical variability of chronic thromboembolic pulmonary hypertension (39)

Case 8 had no macroscopic pulmonary thromboemboli but microscopical investigation was not performed and he cannot be classified with certainty since pulmonary microthromboembolism was not excluded In case 14 coagulation abnormalities suggest chronic thromboembolic pulmonary hypertension Findings in the temporal artery biopsy do not exclude previous thromboses in systemic arteries as well and are interesting also on behalf of the hyperplastic intimal changes (fig 2) Biopsy indication of hyperplastic systemic arterial lesions have not been reported earlier in cases of pulmonary hypertension of primary or thromboembolic type although James reported that primary pulmonary hypertension may sometimes be part of a generalized degenerative arteriopathy (21) and systemic arteritides may at times involve pulmonary arteries (see 39) The patient is unusual in other respects too Firstly she represents the very rare case of "holo-hypertension" (12) i e. persisting hypertension in both the systemic and the pulmonary circuits Endocrinologic investigations relating to this such as urinary mandelic acid determinations (10) have been negative Secondly there are several indications in the patient of an adjoining infectious disease Thrombocytopenia (46) slight monocytosis signs of hepatopathy and polyclonal IgM-increase all are consistent with cytomegal virus infection (3) Since the patient appeared for investigation long after her symptoms started, only convalescent sera for cytomegalvirus serology were obtained.

They exhibited lasting titres of 1/256 So far cytomegalvirus isolation has been negative Also case 10 had persisting positive cytomegalvirus serology in titre 1/256 and we are presently observing an additional case of recurrent pulmonary thromboembolism with convalescent cytomegalvirus titre of 1/256 These findings are inconclusive since positive cytomegalvirus titres are common in the population although not of the magnitude observed in the above cases (36) Cytomegalvirus may be associated with a wide variety of disease manifestations however including "many of the clinical and serologic manifestations observed in some of the auto-immune disorders" (3) A prospective study of cytomegalvirus in thromboembolic diseases might be warranted and has been started.

II. Some frequen y data

13 cases among 1 288 patients subjected to right heart catheterization in the 20-year material broadly correspond with the range of 0 25-1 % given for primary and hronic thromboembolic pulmonary hypertension in earlier right heart catheterization materials (see 29) In the adult cases of primary pulmonary hypertension, females preponderated which is also in accordance with earlier findings (28) On the whole cases of verified chronic thromboembolic pulmonary hypertension were fewer than cases classified as primary pulmonary hypertension. This conflicts with findings in other materials (12 16 39 45) However preliminary data from an autopsy study which we are presently undertaking suggest that heart catheterization is not commonly included in the linical investigation of cases of chronic pulmonary thromboembolism unless they are specifically sought for (45) In a 6-year material (1966-1971) of 8594 autopsies at the General Hospital in Malmö representing some 40 % of all deaths in Malmö and 96 % of the hospital deaths during this time we found 22 cases of widespread chronic pulmonary thromboembolism This gives a frequency of 2 6 ‰ Corresponding figures in two earlier in epidemiological respects not quite comparable materials were 1 5 (20) - 2 ‰ (2) None of the cases in our 6-year material had been subjected to cardiac catheterization.

III. Natural history

Re-catheterization was performed in 6 of the patients (3 5 9 10 12 14) Cases 7 and 11 were follow-up-investigated in 1971 but have refused recatheterization. Concluding clinical histories heart catheterization findings and other investigative data different patterns regarding the pulmonary hypertension emerge in the material

a) Rapid onset and progression. This was the most common course as to a varying degree illustrated by cases 1 2 4 5 6 8 12 and 13 In case 14 the symptomatologic onset was als relatively rapid but the observation time is too short to permit predictions f r the future The catheterization findings had somewhat improved in 1971 and she is presently in a relatively well-controlled state

b) Slow onset and progression, It is true that case 3 was pronouncedly ill during puberty but spontaneous improvement appears to have taken place and she remained relatively well afterwards until the last few years when deterioration has again started. She is till living however some 35 years after the debute of the disease whi h is an unusually long survival in idiopathic pulmonary hypertension (28)

c) Stable condition? The pulmonary hyper tension has remained stable in case 9 and symptomatologically also in case 11 By diagnostical criteria case 7 belongs to the group of idiopathic pulmonary hypertension. Her disease duration seems to be unpreceeded (28)

d) Regression. This course is exemplified by case 10 who improved hemodynamically and clinically Her pulmonary hypertension was very mild however It is well-known that lasting pulmonary hypertension may not develop in all cases of recurrent pulmonary thromboembolism (29)

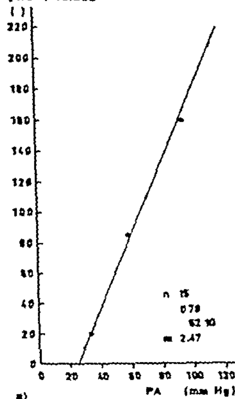
IV Symptoms signs and investigative findings

a) Symptoms and signs Corresponding with findings in earlier materials exertional dyspnea was the prevailing symptom (13 15 16 17 18 24 34 37 45 47) to a varying degree present in all cases Intermittent ankle oedema was not uncommon (15 17 18 37) while stationary oedema dyspnea at rest and hepatomegaly occurred in the cases with the most pronounced pulmonary hypertension. Cyanosis was of peripheral type (18 24 34 37 45) usually not accompanied by finger-clubbing (13 37 47) and was observed to increase on exertion in some of the cases (37) *Hoarseness* (18 47) or hemoptyses (17 18 45 47) were not recorded. Anginous chest pains by some authors ascribed to stretching of the pulmonary arteries (45 47) or to myocardial ishemia (15 45) were usually provoked by exercise (24 37 45) as were syncopal attacks (13 47) The latter are known to be rather common, particularly in severe cases and have been suggested to be due to a critically low cardiac output (37 47) lesions in arteries supplying the sinus and AV nodes (13 15) or reflex mechanism from neuroreceptors in the pulmonary artery with the vagus nerve as afferent path way (11 16) The same factors or malignant arrythmias (13 45) might be responsible for sudden death, too which is a well-documented eventuality in primary and chronic thromboembolic pulmonary hypertension (13 45) *Perhaps low cardiac* output secondary to pulmonary vascular obstruction might appear to be the most plausible of the factors since there were several other manifestations of peripheral vascular insufficiency in many of the cases within the material Most drastically it was expressed in terms of mental confusion slight uremia cutaneous ulcerations and/or systolic blood pressure falling to shock-levels during the final stages of the disease in those patients who did not have a sudden death. Cold blue hands (46) and faint peripheral pulses (46) are common findings The systemic pulse amplitude was low in most cases in the present series with a low or low normal systolic blood pressure and a relatively high diastolic blood pressure suggesting compensatory vaso-regulatory mechanisms Also the symptoms of whitening and numbness of the peripheral extremities on cold exposure in cases 3 7 and 12 might be interpreted as long term consequences of decreased peripheral circulation. Genuine Raynaud s syndrome was present but in case 13 who illustrates the often clear-cut relation of 'primary pulmonary hypertension and Raynaud s phenomenon to systemic sclerosis (see 43) Other well-known, but unspecific symptoms of pulmonary hypertension observed in some of the cases in the material include fatigue (13 45) *feeling of reduced physical capacity* nervousness (13) cardiac palpitations and tachycardia (15) Preceeding febrile illness (39) was not recorded in any of the cases of primary pulmonary hypertension but in three of the cases of verified or suspected chronic thromboembolic pulmonary hypertension (cases 4 10 and 14) It may possibly be a manifestation of otherwise silent disseminated thromboembolization. Actual infectious disease cannot be excluded altogether however

(Presystolic) jugular venous pulsations (13 15 24 34 47) right ventricular lift (13 15 17 34 45 47) accentuated and split pulmonic heart sound (13 15 17 34 37 45 47) and systolic heart murmur along the left sternal border or over the apex (13 15 17 24 37 47) are commonly recorded signs The origin of the systolic murmur did not correspond with hemodynamically significant tricuspid incompetence at the time of catheterization in any

of the cases in the present series and other explanations might be pulmonary ejection murmur (46) or perhaps vibrational phenomenons in a high-pressure right ventricle The diastolic murmur with P M over the pulmonary area noted in some of the cases with pronounced pulmonary hypertension in the material is probably of Graham Steell type (17 34 37 46)

b) Investigative findings These will be briefly commented upon in relation mainly to possible application in the differential diagnosis between primary and chronic thromboembolic pulmonary hypertension. Of course phonocardiograms (fig 3) and electrocardiograms (fig 4) related to the pulmonary hypertension rather than to its underlying cause In the electrocardiograms particularly the QRS-T-angle (14 15) offered a rather satisfactory correlate to the level of pulmonary arterial pressure increase (fig 9a and b) Otherwise findings in the present series correspond with earlier reported. Sinus rhythm was the rule (15 17 37 47) and atrio-ventricular or bundle branch block was not common (15).



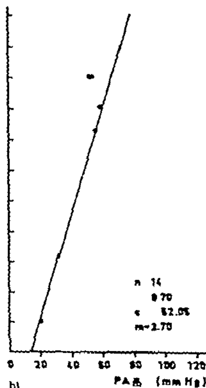


Fig 9 (Abbreviations n = numbe of observations r = correlation coefficient c intercept on y coordinate m = slope of regression line)
Relation of QRS-T-angle to pulmonary arterial pressures in cases 2-14 in the material a Pulmonary arterial systolic pressures ($p < 0.001$)
b Pulmonary arterial mean pressures ($p < 0.01$)

although an impression of incomplete right bundle branch block appeared in some of the cases probably as a consequence of hypertrophy of crista supraventricularis (33) rather than of true conduction delay *Signs of right ventricular* hypertrophy were usually seen (13 37 45 47) When present, pulmonary P-waves were typical but did not occur in the majority of cases (13 24) It is well-known, that T-wave inversions may extend to leads reflecting posterio-anterior forces in pulmonary hypertension (17 24) under which circumstance it is uncertain whether they actually reflect left ventricular in addition to right ventricular strain (7) It is possible, that left ventricular failure may sometimes occur in various types of cor pulmonale (31) T-wave inversion in lead V_7 occurred only in case 9 however (40)

Chest roentgenograms (table 2) were also typical of pulmonary hypertension (13 17 24 34 47) in most cases in the material but did not differentiate between primary and chronic thromboembolic varieties Similarly angiographic investigations which have been claimed to be helpful in this differentiation in some instances (45) in the present series exhibited rather uniform changes relating mostly to the pulmonary hypertension, with right ventricular dilatation and hypertrophy wide central pulmonary arteries narrowing of peripheral pulmonary arteries predominantly from the third branching generations and slow contrast passage through the lungs (13 17 24)

Spirometric findings in case 2 were probably related to his pulmonary disease and in case 9 in 1971 to intrathoracal *space-occupation by her enormous pulmonary* arterial aneurysm (40) In the other cases vital capacity was normal or *slightly reduced (13 15 37 45) N_2-*time normal (45) and particularly in the cases with severe pulmonary hypertension *there was a tendency to low MVV_F* and $FEV_{1.0}$ sometimes in association with increased FRC and RV and slightly *increased or normal TLC Signs of re*duced oxygen diffusion in spite of hyperventilation with low or low normal PaO_2 and $PaCO_2$ (13 17 24 37 45) *were also seen* in many instances On the whole these abnormalities were not more pronounced in *cases with known or suspected chronic* thromboembolic pulmonary hypertension than in those with primary pulmonary hypertension which is at some variance with a few earlier observations (29)

Routine laboratory analyses (table 6) mainly demonstrated polyglobulia in some of the cases (13 17) and, in cases with pro*nounced or advanced pulmonary hypertension*, indications of liver stasis and slight presumably prerenal uremia. It may de*serve mentioning that all cases who had* increased serum LDH (cases 3 12 14) exhibited a similar iso-enzyme pattern with elevation of the fractions 1 2 and 3 and not of the liver fraction, iso-enzyme 5

Coagulation analyses (table 7) perhaps gave the most interesting result in the material It is known that increased thrombocyte *adhesivity may occur both in primary and* chronic thromboembolic pulmonary hypertension (17 29) In our material it was *observed in three cases (case 3 in 1969* case 12 and 13) all of whom were of primary type. Interestingly case 12 and 13 *also exhibited slightly increased fibrinolytic* inhibitors Case 4 10 and 14 had similar but more pronounced thrombosis-pre*disposing" abnormalities Further studies* are needed in order to determine whether distinctive quantitative or qualitative *pattern-differences exist in detailed* coagulation analysis between cases of primary pulmonary hypertension and chronic tromboembolic pulmonary hypertension.

Exercise tests in 8 of the cases (table 5) are represented in order to illustrate the reduced physical capacity in most cases and the increase in pulse rate as well as in breathing frequency commonly observed on exertion.

Heart catheterization findings (table 4) included right atrial a wave no signs *of hemodynamically significant tricuspid*

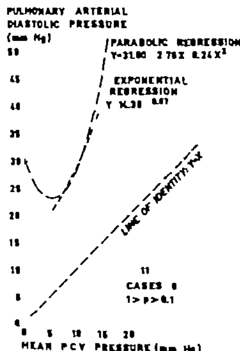


Fig 10 The relation of pulmonary arterial diastolic pressures to PCV pressures in the material expressed in exponential and parabolic regression

incompetence increased right ventricular end-diastoli pressure in many cases with pronounced pulmonary hypertension (15 47) and in the cases in which it was obtained normal or lightly increased PCV-pressure with an obvious pulmonary arterial diastolic pressure gradient against it (fig 10) It is well-known that PCV-pressures are often hard to measure in severe pulmonary hypertension (13 37 47) Cardiac output was commonly low in the investigated cases (37 47) and PVR indexes increased

V Ther peuti al note

Symptomatic medical regimen various pulmonary arterial pressure lowering drugs (24 34, 37 47) vaso-dilating agents (17 37) organic nitrates (1) anticoagulants (13 24 37 45) salicylates against increased platelet adhesivity (29) and even surgical treatment such as pulmonary sympathectomy (13) vena cava ligation (13 45) and banding of the pulmonary artery combined with creation of a systemic-pulmonary artery shunt (37) have been advocated in primary and chronic thromboembolic pulmonary hypertension, but long-term results have not markedly improved. Recently fibrinolytic treatment has been introduced in pulmonary hypertension of chronic thromboembolic as well as of primary type (6 24) In patients where decreased vessel wall fibrinolytic activity has been demonstrated phenformin end ethyloestrenol might be tried, since it has been shown that they may increase vessel wall plasminogen activators (19) This combination was instituted in case 14 but the patient has refused to continue upon the regimen.

In chronic obstructive lung diseases long-term oxygen administration has been shown to improve pulmonary hypertension signi ficantly (see 22) Since there i a desperate need of new treatment" (37) of severe pulmonary hypertension of other causations a trial with continuous oxygen administration was undertaken in a limited series of patients including case 12 in the present material (26) No rtain improvement occurred, howeve (22) A successful treatment of primary and chronic thromboemboli pulmonary hypertension still remains to be found

SUMMARY

Case histories heart catheterization findings and results in performed electrocardiographic phonocardiographic roentgenologic spirometric ergometric laboratory and coagulation investigations in a material of 14 cases of primary and chronic thromboembolic pulmonary hypertension are reported, and discussed in relation to the pertinent literature. Patho-anatomic findings in necropsied cases within the material are briefly described.

REFERENCES

1 Aviado D M. Folle L.E and Bellet S Cardiopulmonary effects of glyceryl trinitrate and isosorbide trinitrate Cardiologia 52.287 1968

2 Ball K P Goodwin J F and Harrison C V : Massive thrombotic occlusion of the large pulmonary arteries Circulation 14:766 1956

3 Barnett, E V Bluestone R Cracchiolo A, Goldberg L.S Kantor G L. and Mc Intosh, R M.: Cryoglobulinemia and disease Ann. Intern. Med 75:95 1970

4 Beuren A.J Hort W Kalbfleish H Müller H and Stoermer J : Dysplasia of the systemic and pulmonary arterial system with tortuosity and legnthening of the arteries A new entity diagnosed during life and leading to coronary death in early childhood Circulation 39.109 1969

5 Beuren A.J Schultze C Eberle D Harmjanz D and Apitz, J The syndrome of supravalvular aortic stenosis peripheral pulmonary stenosis mental retardation and similar facial appearance Amer J Cardiol 13-471 1964

6 Bouvier C A, Ritschard J Meykadeh, F Fournet P and Durhosal P W Traitement fibrinolytique de l hypertension pulmonaire sévère Justification modalités et critique Schweiz Med, Wschr 100.148 1970

7 Causey W A. Felts S K and Blake T M. Electrocardiography in the evaluation of right ventricular overload Southern Med. J 62.166 1969

8 Coelho E de Paiva E and Nunes A.: Malformations of the pulmonary artery and its branches including two cases of absence of the right pulmonary artery Angiocardiographic and hemodynamic study Amer J Cardiol 13-462 1964

9 Dankmeijer J Herles F Ibrahim M Reid D D Richards D W Stuart Harris C H Taquini A.C and Werkö L. Chronic cor pulmonale Report of an expert committe. Circulation 27:594 1963

10 Degenring F H.: Die unterschiedliche Wirkung von Noradrenalin and Adrenalin auf den Lungenkreislauf Arch Kreislaufforsch. 62:181 1970

11 Dressler W : Effort syncope as an early manifestation of primary pulmonary hypertension Amer J Med Sci 223.131 1952

12 Evans W : The less common forms of pulmonary hypertension. Brit. Heart J 21.197 1959

13 Fowler N O Black-Schaffer B Scott R.C and Gueron, M. Idiopathic and thromboembolic pulmonary hypertension. Amer J Med 40:331 1966

14 Fowler R.S. and Keith J D : The electrocardiogram in pulmonary stenosis - A reappraisal Canad Med. Ass J 98 433 1968

15 Gahl K Fabel H Greiser E Harmjanz D Ostertag H. and Stender H St.: Primär vaskuläre pulmonale Hypertonie Z Kreislaufforsch. 59:868 1970

16 Goodwin, J F Harrison C V and Wilcken D E L.: Obliterative pulmonary hypertension and thrombo-embolism Brit Med J 1 701 1963

17 Gurtner H P Gertsch M. Salzmann, C Scherrer M. Stucki P and Wyss F : Häufen sich die primär vasculären Formen des chronischen cor pulmonale? Schweiz Med. Wschr 98:1579 and 1695 1968

18 Heath, D Whitaker W and Brown, J W : Idiopathic pulmonary hypertension. Brit. Heart J 19:83 1957

19 Isacson, S and Nilsson, I. M. : Effect of treatment with combined phenformin and ethyloestrenol on the coagulation and fibrinolytic systems Scand. J Haemat. 7 404 1970

20 Jacobsson K A. Koch, G and Lilieqvist B : Multiple pulmonary artery aneurysms Acta. Med. Scand. 179-673 1966

21 James T N Degenerative arteriopathy with pulmonary hypertension: a revised concept of so-called primary pulmonary hypertension. Henry Ford Hosp Med. Bull 9:271 1961

22. Johansson, B W Torp A. and Trell E Prolonged ambulatory oxygen therapy in pulmonary hypertension of various etiology Acta. Med. Scand. 189:155 1971

23 Kaindl F Kotscher E and Lobenwein, E Zur Radiologie pulmonalen Gefässfehlbildungen. Radiologe 11:169 1971

24. Krähenbühl, B Laperrouza, C and Moret, P L hypertension pulmonaire essentielle" ou "thrombo-embolique Etude de cinq observations Schweiz Med. Wschr 98.1311 1968

25 Lees M. H. Menashe V D Sunderland C D Morgan, C L. and Dawson, D J Ehlers-Danlos syndrome associated with multiple pulmonary artery stenoses and tortuous systemic art ries J Pediat. 75:1031 1969

26 Malmqvist, J Trell E. Torp A. and Lindström C. : A case of drug-induced (?) pulmonary hypertension. Acta. Med. Scand. 188;265 1970

27 Mc Donald, A H Gerlis L. M. and Somerville J Familial arteriopathy with associated pulmonary and systemic arterial stenosis Brit. Heart J 31;375 1969

28 *Mc Kusick, V A. The cardiovascular* aspects of Marfan syndrome: Heritable disorder of connective tissue Circulation 2.321 1955

29 Oakley C M. and Goodwin, J F : Current clinical aspects of cor pulmonale Amer J Cardiol 20:842 1967

30 Owen W R Thomas W A. Castleman B and Bland E F : Unrecognized emboli to the lungs with subsequent cor pulmonale New Engl. J Med. 249:919 1953

31 Rao B. S Cohn, K. E Eldridge F L. and Hancock, E W Left ventricular failure secondary to chronic pulmonary disease. Amer J Med. 45 229 1968

32 Rotman M. Morris J J Behar V S *Peters R. H. and Kong* Y Aortic valvular disease. Comparison of types and their medical and surgical management. Amer J Med. 51;241 1971

33 Schamroth, L. : The electrocardiographic manifestations of right ventricular dominance S. Afr Med. J 41;119 1967

34 Shane S J Aterman, K Roy D L. and Chandler B M. : Primary pulmonary hypertension. A review and report of five cases Canad. Med. Ass 91;145 1964.

35 Singleton, E B Leachman R. D and Rosenberg H. S Congenital abnormalities of the pulmonary arteries Amer J Roentgen. 91:487 1964.

36 Stormby K. : Personal communication.

37 Storstein, O Efskind L., Müller C Rokseth R. and Sander S : Primary pulmonary hypertension with emphasis on its etiology and treatment Acta Med. Scand 179:197 1966

38 Trell E : Benign, idiopathic pul monary hypertension? Report of two further cases of unusually long duration. In preparation.

39 Trell E : Primary and chronic thromboembolic pulmonary hypertension. Nosologic spectrum In preparation

40 Trell E : Pulmonary arterial aneurysm With remarks on pulmonary hypertension natural history and possible disturbance of pulmonary parenchymatous function. In preparation.

41 Trell E : Pulmonary hypertension in lung disorders Observations in a heart catheterization material Acta. Med. Scand In press

42 Trell E Johansson, B W Andrén, L. and Ohlsson N -M.: The scimitar syndrome With particular reference to its pathogenesis Z Kreislaufforsch. 60:680 1971

43 Trell, E and Lindström C Pulmonary hypertension in systemic sclerosis Ann. Rheum. Dis 30:390 1971

44 Wagenvoort C A. and Wagenvoort N : Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases Circulation 42:1163 1970

45 Wilhelmsen, L. Selander S Söderholm B Paulin, S Varnauskas E and Werkö L.: Recurrent pulmonary embolism Medicine (Balt.) 42 335 1963

46 Wood P : Primary pulmonary hypertension In: Diseases of the heart and circulation. p 839 Eyre & Spottiswoode London, 1956

47 Yu, P N : Primary pulmonary hypertension. Report of six cases and review of literature Ann. Intern. Med. 49:1138 1958

48 Zuelzer W W Mastrangelo R. Stulberg, C S. Poulik, M.D Page R.H. and Thompson, R I : Autoimmune hemolytic anemia Natural history and viral-immunologic interaction in childhood Amer J Med 49:80 1970

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Studies on Pulmonary Hypertension

1. Pulmonary hypertension in congenital shunt defects
2. Pulmonary hypertension in lung disorders

Observations in a heart catheterization material

By Erik Trell

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STUDIES ON PULMONARY HYPERTENSION

Observations in a heart catheterization material

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I. PULMONARY HYPERTENSION IN CONGENITAL SHUNT LESIONS

Observations in a right heart catheterization material with particular reference to occurrence natural history and prognostic implications in adolescence and adulthood.

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Supplementum 535

INTRODUCTION

"Pulmonary arteriosclerosis" (atherosclerosis arteriolosclerosis) was known to occur in congenital shunt lesions ventricular septal defect (VSD) (44) persistent ductus arteriosus (PDA) (11) as well as atrial septal defect (ASD) (77) already in the beginning and middle of the nineteenth century (see 60) The relation of pulmonary arteriosclerosis to "allen denjenigen Zuständen welcher mit einer Drucksteigerung in kleinen Kreislauf verbunden sind" (48) was well understood (60) After early animal experimentation (4 6 46 51) and pioneering human application (31) safe and reliable routine techniques of right heart catheterization in man were developed by Cournand and associates (19 20) and hemodynamic studies of pulmonary hypertension in congenital shunt lesions soon appeared (2 5 8 12 21 23 26 27 28 30 33 40 53 69 75 78 79) Now there is an extensive literature of pulmonary hypertension in shunt lesions of intracardiac (2 9 10 13–16 18 22 25 29 34 35 39 45 47 49 50 55–59 61 64 66 70 71 80) as well as of extracardiac varieties (7 10 17 32 37 38 42 64 68 72 73) None the less in a recent review concerning ventricular septal defect it was stated that most of the evidence concerning pulmonary hypertension in this disorder is limited to the first decade of life and that observations at later ages are badly needed" (16) To some extent the same may apply also to other varieties The purpose of the present paper is to report some aspects of pulmonary hypertension particularly relating to hemodynamic patterns prognostical implications in terms of rude mortality and survival and findings in re-catheterisations in a total right heart catheterization material of intracardiac shunt lesions including a fair number of adult cases of ASD VSD and PDA and also a limited series of extracardiac hunt varieties with a brief discussion of the findings in relation to some of the pertinent literature

MATERIAL AND METHODS

The material consists of 101 cases of atrial septal defect 76 cases of ventricular septal defect 85 cases of persistent ductus arteriosus 15 cases of complex congenital intracardiac shunt defects and 18 cases of various types of extracardiac shunt lesions subjected to right heart catheterization according to routine techniques not further described here at the Heart Laboratory Malmö General Hospital during the 20-year period from the 3rd quarter of 1948 until the 4th quarter of 1968 The composition of the material is represented in table 1 Many of the patients were subjected to re-catheterization and in the table, only data from the catheterization with the highest pulmonary arterial pressures are utilized while other re-catheterization findings are separately described (fig 2 and 3) Pulmonary arterial systolic pressures ≤ 30 mm Hg were considered normal (16) between 31–40 mm Hg they were regarded slightly elevated" while pressures ≥ 41 mm Hg were subclassified in consecutive steps of 20 mm Hg into moderate (41–60 mm Hg) pronounced (61–80 mm Hg) and severe (≥ 81 mm Hg) pulmonary hypertension. Right ventricular systolic pressures were included in a few cases without indications of right ventricular outflow obstruction in whom pulmonary arterial pressures were not obtained. Cases with significant co-existing pulmonary stenosis were excluded from the material.

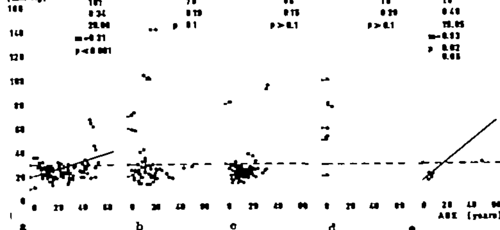


Fig 1 (Abbreviations in this and following figures n = number of observations r = correlation coefficient c = intercept on y-coordinate m = slope of regression line p = probability Like in the following figures the regression line is not represented if $p \geq 0\ 1$)
Relation between pulmonary arterial systolic pressures and patient ages
a. Atrial septal defect (x = previously operated) b Ventricular eptal defect.
c Persistent ductus arteriosus d. Complex intracardiac shunt lesions
e Extra cardiac shunts (x = A case of the Scimitar syndrome with associated endocardial cushion defect)

FINDINGS

No further subclassification was undertaken in the tabular (table 1-2) and hemodynamic (fig 4-6 9-10) representation of the atrial septal defect, ventricular septal defect and persistent ductus arteriosus groups Similarly complex intracardiac shunt lesions including 7 cases of transposition of the great vessels one case of corrected transposition of the great vessels 4 cases of persistent truncus arteriosus and 3 cases of common ventricle were considered together in one group while in table 1 2 extracardiac shunt lesions are furthe subdivided into four subgroups

a) Patient data

In all groups except for in the cases with complex intracardiac shunt defects females preponderated over males; most markedly in persistent ductus arteriosus and in atrial septal defect (table 1) The sex difference was m re pronounced in cases with normal pulmonary arterial pressures than in cases with pulmonary hypertension however (table 1)

Age did not differ significantly between cases with normal pulmonary arterial systolic pressure and cases with pulmonary hypertension in ventricular septal defect and in persistent ductus arteriosus (table 1 fig 1b-c) Complex intracardiac shunt lesions with few exceptions were infants (table 1 fig 1d) while in atrial septal defect and in the extracardiac shunt group cases with pulmonary hyper-

Table 1

Disease	Total				Normal PA systolic pressure (≤ 30 mm Hg)				Sum pulmonary hypertension (≥ 31 mm Hg)			
	Number		Age		Number		Age		Number		Age	
	♀	♂	m̄	sd	♀	♂	m̄	sd	♀	♂	m̄	sd
I Atrial septal defect	65	36	26.1	15.5	49	26	24.1	13.9	16	10	22.1	10.4
II Ventricular septal defect	43	35	14.7	11.3	29	18	14.2	10.7	18	17	15.6	12.2
III Persistent ductus arteriosus	67	18	15.4	11.6	49	12	13.9	10.1	18	6	19.2	14.6
Sum I, II and III	175	89	19.3	14.2	126	56	18.2	12.9	49	33	21.9	16.5
IV Others (unassociated with pulmonary stenosis)	6	9	4.0	8.6	1	1	3	(4.8)	5	8	4.1	5.9
Sum I, II, III and IV	181	98	18.5	14.3	127	57	18.0	12.9	54	41	19.1	16.4
V Extra-cardiac shunts												
a) Systemic arterio-venous fistula	3	1	51.3	6.3	1	1	56	(0.7)	2	0	46	(2.0)
b) Pulmonary arterio-venous fistula	2	2	20.3	19.2	2	1	11.0	6.1	0	1	49	
c) Anomalous pulmonary venous return	4	3	12.9	13.1	4	3	12.9	13.1	0	0		
d) Scimitar syndrome	2	1	44.0	5.6	0	0			2	1	44.0	5.6
Sum V a-d	11	7	23.3	20.5	7	5	19.7	19.9	4	2	45.6	4.2
Sum I, II, III, IV and V	192	105	19.1	14.9	134	62	18.1	13.4	58	43	21.0	17.3

Table 1: (Abbreviations m̄ = mean, sd = standard deviation)
Sex and age (years) of patients and the various disorder groups in the material. The table gives number of females and males in the various groups and pulmonary arterial pressure levels while age of patients includes both sexes. The age range is not represented. The table is divided into three sections: to the left all cases within the various disease groups are summed up. In the middle section those with normal pulmonary arterial systolic pressures are compared with the sum of patients with various degrees of pulmonary arterial pressure increase, and to the right the latter patients are subdivided in consecutive levels of pulmonary hypertension.

Slightly elevated PA syst. pressure (31–40 mm Hg)				Moderate pulmonary hypertension (41–60 mm Hg)				Pronounced pulmonary hypertension (61–80 mm Hg)				Severe pulmonary hypertension ($\geq$ 81 mm Hg)				Pulmonary art. syst. pressure	
Number		Age		Number		Age		Number		Age		Number		Age			
♀	♂	$\bar{m}$	sd	♀	♂	$\bar{m}$	sd	♀	♂	$\bar{m}$	sd	♀	♂	$\bar{m}$	sd	$\bar{m}$	range
7	8	23,5	18 4	3	4	30 4	19 2	6	1	41,6	9 7	1	0	37		160	(160)
1	4	15 0	12,4	2	3	7 1	9 2	2	2	10 1	12,2	10	8	19 2	12.1	109 2	85–142
7	2	18,8	13 5	3	1	32,3	22,3	2	0	16	(0 7)	6	3	17 5	21,9	109 3	61–131
15	11	18 7	16,6	8	8	27 5	21,9	9	3	27 8	18 1	17	11	19 3	12.1		
0	1	8		1	3	6,2	0 2	2	2	3,9	3.6	1	1	10	(12.8)	90	90–100
15	12	18 2	16 4	9	11	22,1	22,6	12	6	19 3	18 6	18	12	18 7	13 2		
0	0			0	0			0	0			2	0	46	(2,8)	107 5	90–117
0	0			0	1	40		0	0			0	0				
0	0			0	0			0	0			0	0				
1	1	43	(7 8)	0	0			0	0			1	0	45		133	(133)
1	1	43	(7 8	0	1	43		0	0			3	0	48.7	2.1		
16	13	20 1	16 3	9	18	23,4	22,7	12	6	19 3	18 6	21	12	21.1	14.0	108 7	61–142

tension tended to be older than cases with normal pulmonary arterial systolic pres sure (table 1 fig 1a c)

b) Survival and mortality

Crude survival and mortality from the time of catheterization to the autumn of 1971 or longer were followed up in all patients in the material. Information could not be obtained in 7 cases The results are summarized in table 2 Among 196 cases with normal pulmonary arterial systolic pressures in the total material, there were only 8 deaths; 2 patients were lost for follow-up Among 101 cases with pulmonary hypertension in the whole material there were 48 deaths and 5 were lost for follow-up A tendency towards increasing mortality with increasing pulmonary arterial pressures is also apparent

Table 2

Disease (the same groups as in table 1)	Total				Lost for follow up	Normal PA systolic pressure (≤ 30 mm Hg)				Lost for follow up	Sum pulmonary hypertension (≥ 31 mm Hg)				Lost for follow up
	Surviving		Dead			Surviving		Dead			Surviving		Dead		
	nr	time	nr	time		nr	time	nr	time		nr	time	nr	time	
I	90	10 6	11	6 1	0	73	10 8	2	6	0	18	9 8	9	6 1	0
II	58	11.9	18	4 0	5	43	11 3	2	4.5	2	13	12 7	16	3.9	3
III	73	13.6	11	2.5	1	60	13.1	1	10	0	13	16 1	10	1.6	1
Sum I–III	218	11 9	40	4 2	6	175	11 6	5	6 2	2	43	12.9	35	3.0	4
IV	5	10.0	9	0.13	1	1	14	1	0 03	0	4	9 0	8	0 13	1
Sum I–IV	223	11.9	49	3.4	7	176	11 7	6	5.2	2	47	12.8	43	3.2	5
V															
a)	1	4	3	1 2	0	1	4	1	0.5	0	0		2	1 5	0
b)	3	10 7	1	2	0	3	10 7	0		0	0		1	2	0
c)	6	11 7	1	0 25	0	6	11 7	1	0.25	0	0		0		0
d)	1	11	2	2	0	0		0		0	1	11	2	2	0
Sum V a–d	11	10 6	7	1 4	0	10	10 6	2	0.4	0	1	11	5	1.6	0
Sum I–V	234	11.6	56	3 2	7	186	11.6	8	4 9	2	48	12.4	48	3.3	5

Table 2 (Abbreviations nr number of cases, "Time" stands fo the mean duration of survival from the time of catheterization, or the mean time until death after the time of catheterization (years) while range and standard deviation re not given.)
In the table which contains the same groups as table 1 results of follow-up investigation regarding survival and mortality of the cases in the material up to the autumn of 1971 re represented. For matters of brevity it is not separated between females and males

(table 2) Age may have been a factor of some significance for this increasing mortality in the atrial septal defect and the extracardiac shunt lesion groups since patients with pulmonary hypertension tended to be older in these than patients with normal pulmonary arterial systolic pressures As can be seen from fig 1a and e there were however also many cases in the higher ages with normal pulmonary arterial pressures in these groups and with one exception they have all survived The two patients who died among the patients with normal pulmonary arterial systolic pressure in the atrial septal defect group were a 20-year old woman who died at re-operation and a 23-year old woman who died of non-cardiac cause The two cases of extracardiac shunt lesion and normal pulmonary arterial pressures who have expired were a girl 5 months of age with total anomalous pulmonary venous return and pulmonary arterial systolic pressure of 30 mm Hg who died at operation; and a 56-year old woman with Osler s disease and pronounced pulmonary arteriovenous fistula formation, who died in the picture of left heart failure Since age did not differ significantly between the various pressure levels in the other disorder groups it would follow that age per se did not influence the different mortality in them

Slightly elevated PA syst. pressure (31 40 mm Hg)				Lost for follow up	Moderate pulmonary hypertension (41 60 mm Hg)				Lost for follow up	Pronounced pulmonary hypertension (61 80 mm Hg)				Lost for follow up	Severe pulmonary hypertension ($\geq$ 81 mm Hg)				Lost for follow up
Surviving		Dead			Surviving		Dead			Surviving		Dead			Surviving		Dead		
nr	time	nr	time		nr	time	nr	time		nr	time	nr	time		nr	time	nr	time	
0	11,8	3	4,4	0	6	7 8	1	12	0	2	10	4	8 3	0	0		1	9	0
3	12,0	2	0,07	0	2	9 8	2	0,14	1	1	22	3	1,0	0	7	14,0	3	6 6	3
7	13 0	1	0,04	1	3	10,3	1	7	0	2	13	0		0	1	10	8	1,4	0
19	14,4	6	2,3	1	11	8,6	4	4,8	2	5	12,6	7	2,4	0	8	14,6	18	4,4	2
1	16	0		0	0		4	0,13	0	2	6 8	3	0 13	1	1	7	1	0,17	0
20	14,5	6	2,3	2	11	8 6	8	2,5	1	7	11 6	10	2,4	1	9	12,6	19	4,2	2
0		0		0	0		0		0	0		0		0	0		2	1,6	0
0		0		0	0		1	2	0	0		0		0	0		0		0
0		0		0	0		0		0	0		0		0	0		0		0
1	11	1	8	0	0		0		0	0		0		0	0		1	1	0
1	11	1	3	0	0		1	2	0	0		0		0	0		3	1 3	0
21	12,3	7	2,4	1	11	8 6	9	2,4	1	7	11 6	10	2,4	1	9	12,6	22	3,8	2

Results of subsequent surgery might be a more important factor However cases with pronounced and severe pul monary hypertension, especially in the ventricular septal defect group were often not operated In figures 2 and 3 survival graphs including all re-catheterized cases as well as all cases with pul monary hypertension catheterized but once in the material also indicate results of performed operations Cases lost for follow-up and not re-catheterized cases with normal pulmonary arterial pressure are not represented in the figures Like the re-catheterized cases with normal pressure the latter had a good prognosis and inclusion of them would not change the general tendency in the figures It can be seen that there were *a few cases* with pulmonary hypertension in the ma terial in whom cardiac surgery remarkably improved the pulmonary arterial pressure but that, on the other hand, the operative and immediate postoperative mortality was high in this group The figures also indicate that recovery was uneventful after operation in most of the cases with normal pulmonary arterial pressures

c) Re-catheterizations

Performed re-catheterizations in atrial septal defect and in extracardiac shunt lesions are represented in figure 2 and in ventricular septal defect persistent ductus arteriosus and complex intra cardiac shunt defects in fig 3 The findings in these figures are discussed later

d) General hemodynamic findings

The relation between pulmonary arterial pressures and the mean PCV pressure in the various disorder groups in the material is graphically represented in figures 4 7 the last figure concluding the findings in the two smallest groups



Fig 2 (Abbreviations: HHT = hereditary hemorrhagic telangiectasia H = hepatic arteriovenous fistula P = pulmonary arteriovenous fistula S Scimitar syndrome)
Survival graph" of atrial septal defect and extracardiac shunt lesion cases in the material including recatheterized cases and also cases with pulmonary hypertension catheterized but once; but excluding cases lost for follow up and not recatheterized cases with normal pulmonary arterial pressures See text

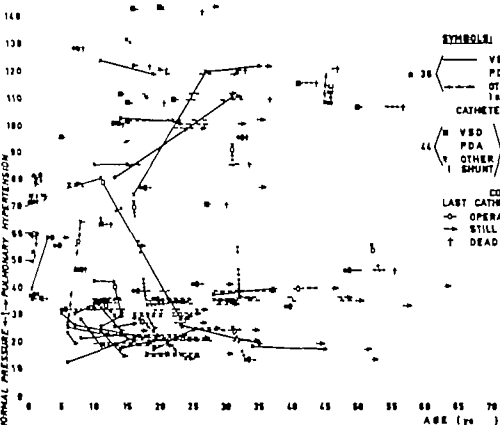


Fig 3 (Abbreviations: S + ECD one case of the Scimitar syndrome and associated endocardial cushion defect)[2]
Survival graph of ventricular septal defect, persistent ductus arteriosus and complex intracardiac shunt lesion cases in the material according to figure 2

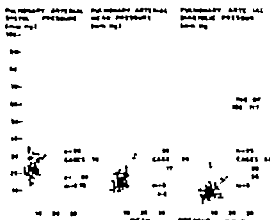


Fig 4 Relation between resting pulmonary arterial pressures and the mean PCV pressure ( ) or left atrial pressure (x) in the atrial septal defect cases
a Pulmonary arterial systolic pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure

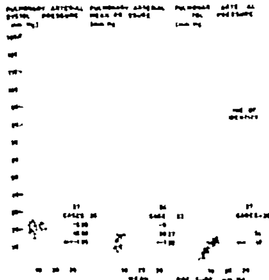


Fig 6 Relation between resting pulmonary arterial pressures and the mean PCV pressure in the persistent ductus arteriosus cases
a. Pulmonary arterial systolic pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure

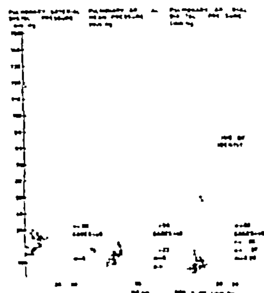


Fig 5 Relation between resting pulmonary rterial pressures and the mean PCV pressure ( ) or left atrial pressure (x) in the ventricular defect cases
a. Pulmonary arterial systoli pressure
b Pulmonary arteri l mean pressure
c Pulmonary arterial di stoli pressure

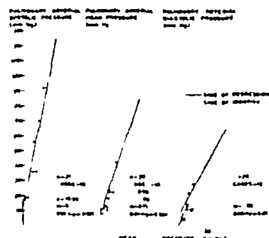


Fig 7 Relation between pulmonary arterial pressures and the mean PCV pressure in the complex intracardiac shunt lesion (x) and the extracardiac shunt lesions case ( )
a Pulmonary arterial systoli pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure

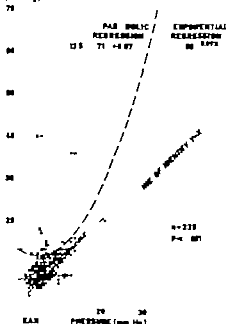


Fig 8 Relation between the pulmonary arterial diastolic pressure and the mean PCV ( ) and/o left atrial (x) pressure (both are represented from an individual patient if obtained) in the total material, as expressed in exponential and parabolic regression equations See text.

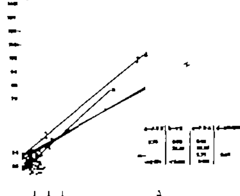


Fig 9 Relation between pulmonary arterial systolic pressure and PVR index in the material. Separate regression lines are given for the atrial septal defect (a) ventricular septal defect (b) persistent ductus arteriosus (c) and other (d) cases (halting slightly after the highest PVR index encountered in the respective groups)

i e complex intracardiac shunt lesions (6 observations) and extracardiac shunt lesions Slight increase of the PCV pressure was not infrequent, predominantly in cases with normal or slightly increased pulmonary arterial pressures In cases with pulmonary hypertension, PCV – left atrial pressures were usually normal, with a marked pulmonary arterial diastolic gradient against them (fig 4–7 c) Linear regression analyses did not prove to be a useful tool in characterizing this gradient. Even if non-linear regression analyses in the whole material gave a somewhat better formular representation (fig 8) it is apparent that in the higher levels of pulmonary hypertension, increased left atrial pressures directly measured or reflected in the PCV pressures tend to play no significant part at all in the maintenance of increased pulmonary arterial diastolic pressures in shunt lesions but that precapillary pulmonary vascular obstruction is the vir-

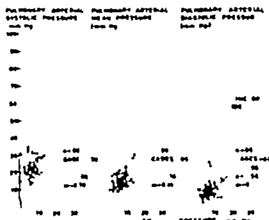


Fig 4 Relation between resting pulmonary arterial pressures and the mean PCV pressure ( ) or left atrial pressure (x) in the atrial septal defect cases
a. Pulmonary arterial systolic pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure



Fig 5 Relation between resting pulmonary arterial pressures and the mean PCV pre sure ( ) or left atrial pressure (x) in the ventricula defect cases
a. Pulmonary arteri l systoli pre sure
b Pulmonary rterial mean pressure
Pulmonary rterial di stolic pressure



Fig 6 Relation between resting pulmonary arterial pressures and the mean PCV pressure in the persistent ductu arteriosus cases
a. Pulmonary arterial systolic pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure

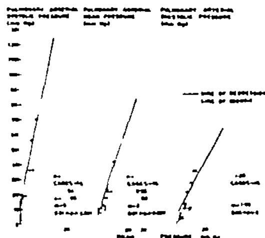


Fig 7 Relation between pulmonary arterial pressures and the mean PCV pressure in the complex intracardiac shunt lesion (x) and the extracardiac shunt le ions cases ( )
a. Pulmonary arterial systolic pressure
b Pulmonary arterial mean pressure
c Pulmonary arterial diastolic pressure



a



b

Fig 11 Corrosion cast preparation of pulmonary arteriovenous fistulae in a cas of Osler s disease (see text) (By courtesy of Associate Professor Jan Nordén, Department of Pathology Malmö General Hospital) a) Several direct large vessel anastomoses near the surface of a lung lobe b) Two anastomoses at loser detail.

sent an interesting type of pulmonary vascula abnormality One, a woman aged 49 years at the first catheterization when he pulmonary arterial systolic pressure was 12 mm Hg had pronounced pulmonary arteriovenous fistula, with a shunt volume of approximately 40 % of the cardiac output. She had increasing arterial oxygen unsaturation, cyanosis and finger clubbing and finally developed signs of predominantly left ventricular decompensation. She was re-catheterized at the age of 56 years when her pulmonary arterial systolic pressure was 22 mm Hg She died 6 months after this catheterization in left heart failure Corrosion cast preparation of the pulmonary vasculature demonstrated wide-spread pulmonary arteriovenous fistula formation (fig 11) The second was a 7-year old girl grand-daughter to the former who had a localized pulmonary arteriovenous aneurysm with an approximate shunt volume of 20 % of the cardiac output. Subsequently the pulmonary arteriovenous aneurysm was successfully surgically removed. Both these cases thus had normal pulmonary arterial pressures while another patient a 40-year old man without family history or external stigmata of Osler disease had a large pulmonary arteriovenous fistula with calculated shunt volume of 40 % of cardiac output and pulmonary arterial pressure of 49/22 mm Hg The three patients may illustrate that pulmonary rterial pressures are usually normal in pulmonary arteriovenous fistula (32, 73) but that pulmonary hypertension can sometimes occur even in this condition (66)

DISCUSSION

There are several recent studies on pulmonary hypertension in congenital cardiac shunt lesions mostly reporting experiences of current facilities of surgical treatment (10 18 23 34 36 45 47 49 52 57 58 61 66 70) The present report summarizes some findings in a 20-year material which also includes a proportion of unoperated cases in particular of ventricular septal defect. Recently the natural history and age-related mortality rates in ASD (15) VSD (16) and PDA (14) were thoroughly surveyed by

Campbell It was thought to be of interest to indicate prognostical implications of pulmonary hypertension in congenital shunt lesions in terms of subsequent cumulative mortality and survival in a material containing a fair number of adolescent and adult patients Operation results and the age of the patients obviously enter into the picture however Figures 2 and 3 may give a summary of the patterns met with.

In the atrial septal defect group (fig 1a 2) few cases presented with pulmonary hypertension before the age of 30 The reinvestigated not previously operated usually symptomatic cases of atrial septal defect in the adult age-groups regularly exhibited further increase of the pressures at the re-catheterization (fig 2) A similar tendency of clustering of cases with pulmonary hypertension in the adult age-groups and of gradual further increase of the pulmonary arterial pressure in one repeatedly re-investigated case was noted in the admittedly small extra cardiac shunt lesion group (fig 2) It seems plausible that the development and hemodynamic features of pulmonary hypertension in many cases of extracardiac shunt lesions may remind of the patterns in atrial septal defect since the shunt is delivered to the right heart under venous pressure in both situations with no direct transmission of systemic arterial pressure between the two heart halves (17 35 4 73) However this does not hold true in all cases since children with pronounced systemic arteriovenous fistula may early develop rapidly progressive cardiac failure (17) as is naturally also the case in total anomalous pulmonary venous return (42)

Most cases of atrial septal defect in the material were operated upon. Fig 2 shows that even in cases 45-50 years of age and with slight to moderate degree of pulmonary hypertension operation usually was successful and that the pulmonary arterial pressures returned to normal levels in the cases re-catheterized after operation. Operation was not performed in three cases of atrial septal defect with pronounced pulmonary hypertension in this age group All of them later expired. There was but one (female) case in the atrial septal defect group who developed really severe pulmonary hypertension with inversed shunt and marked central cyanosis however and in whom operation was clearly contraindicated even according to current surgical standards (55) She died 9 years after the last catheterization at the age of 47 years in severe right cardiac decompensation. Autopsy showed a very large atrial septal defect and extreme organized and recent thrombotic occlusion of the pulmonary arteries It is well-known that "pulmonary embolism and thrombosis are important aggravating factors once pulmonary hypertension has developed in cardiac shunt lesions (30) There is "no evidence that they initiate the pulmonary hypertension" (30) however

The tendencies expressed in fig 2 largely accord with earlier findings (18 30 36 55 64 80) Commonly there is a late development of cardiac failure as well as of pulmonary hypertension both in atrial septal defect (18 30 36 55 64 80) and many varieties of extracardiac shunts such as anomalous pulmonary venous return (42) and systemic arteriovenous fistula (35 73) However large systemic arteriovenous fistula in children may lead to early cardiac failure (17) In atrial septal defect there is in general no correlation between the shunt volume (59 66) – or the anatomic defect size (80) – and the pulmonary arterial pressure Thus the pulmonary blood flow per se is rarely increased enough to call forth momentaneous pressure increase and Wood concluded that many cases may continue to have large blood flow until 50-75 years of age when left ventricular failure will usually occur and that obliterative pulmonary hypertension protractedly develops but in a small number of cases (7 %) in which a powerful hyperkinetic factor comes into being before complete post-natal involution and relaxation of the muscular pulmonary

arteries has taken place (80) Also Oakley and Goodwin concluded that rise of the pulmonary arterial pressure in atrial septal defect is nearly always a late occurrence indicating the development of "an obliterative pulmonary vascular disease with augmented operation risk" (55) Still in the comparatively old patient with moderate degree of pulmonary hypertension, operation will usually be successful however (18 59 66) and operation is regarded contraindicated only in the cases where an inversed shunt has established

In the ventricular septal defect, persistent ductus arteriosus and complex intracardiac shunt defect cases another pattern emerged (fig 1b–d, 3) The complex intracardiac shunt defect cases for natural reasons were predominantly infants and had a serious prognosis Also in VSD and PDA there were infant cases with established pulmonary hypertension, usually showing a poor prognosis with short survival both in unoperated cases and on operation. This serious outlook was apparent in most of the cases where severe pulmonary hypertension was met with under the age of 5–10 years Two main patterns may be discerned when pulmonary hypertension was encountered in subsequent age–groups Re–catheterization in those with pulmonary hypertension around a systolic pressure level of 80 mm Hg or less predominantly showed further increase of the pressure at reinvestigation (6 cases) while cases with systolic pulmonary arterial pressures exceeding 80 mm Hg usually exhibited largely fixed pressures (7 cases) Cases with severe pulmonary hypertension encountered in these age groups usually had mixed or inversed shunts and were according to still largely valid principles (29 34 35) not operated upon. One case of ventricular septal defect, and two cases of persistent ductus arteriosus with pulmonary arterial pressures between 70–90 mm Hg and large shunts were operated upon with satisfactory results however

Furthe it is apparent that very few cases with severe pulmonary hypertension were encountered beyond the age of 35 years One remarkable exception was a 50–year old woman with ventricular septal defect and pulmonary arterial pressure of 106/72 mm Hg who lived to the age of 56 years Even if the follow–up investigation regarding mortality and survival in cases around 10–20 years of age at the first catheterization showed that many of them, in particular ventricular septal defect cases were still alive up till 20 years afterwards and more, the general impression from the material is that (a) pulmonary hypertension usually develops during early life in ventricular septum defect, persistent ductus arteriosus and naturally complex intracardiac shunt defects as compared with in atrial septal defect and in extracardiac shunt lesions (b) the earlier severe pulmonary hypertension is met with, the more serious the prognosis appears to be; (c) cases with severe pulmonary hypertension encountered after the age of 10–15 years in particular of ventricular septal defect may stay alive for a considerable time with a largely fixed pulmonary hypertension but (d) it is unusual to encounter a case with severe pulmonary hypertension still living after the age of 40 and, even more after the age of 50 years (16)

However the first two of these statements require comparison with the patterns met with during infancy Fig 12 summarizes the data available in the literature regarding the ordinary pulmonary arterial pressure relations in man during early post–natal life (1 3 24 26 41 43 62 63 67) It can be seen that in the normal infant, the pulmonary arterial pressure is of systemic magnitude immediately after birth, but rapidly decreases during the subsequent hours and days reaching adult" levels within a week or two In most infants with ventricular septal defect this does not seem to be the case but only in those with quite small shunt size (approximately 1 cm/m^2 BSA or less (49)) and they will almost invariably continue to be normotensive afterwards (2 12) A few cases may fail to show a

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In the atrial septal defect group (fig 1a 2) few cases presented with pulmonary hypertension before the age of 20 The re-investigated not previously operated, usually symptomatic cases of atrial septal defect in the adult age-groups regularly exhibited further increase of the pressures at the re-catheterization (fig 2) A similar tendency of clustering of cases with pulmonary hypertension in the adult age-groups and of gradual further increase of the pulmonary arterial pressure in one repeatedly re-investigated case was noted in the admittedly small extracardiac shunt lesion group (fig 2) It seems plausible that the development and hemodynamic features of pulmonary hypertension in many cases of extracardiac shunt lesions may remind of the patterns in atrial septal defect since the shunt is delivered to the right heart under venous pressure in both situations with no direct transmission of systemic arterial pressure between the two heart halves (17 38 42 73) However this does not hold true in all cases since children with pronounced systemic arteriovenous fistula may early develop rapidly progressive cardiac failu re (17) as is naturally also the case in total anomalous pulmonary venous return (42)

Most cases of atrial septal defect in the material were operated upon. Fig 2 shows that even in cases 45-50 years of age and with slight to moderate degree of pulmonary hypertension operation usually was successful and that the pulmonary arterial pressures returned to normal levels in the cases re-catheterized after operation. Operation was not performed in three cases of atrial septal defect with pronounced pulmonary hypertension in this age group All of them later expired. There was but one (female) case in the atrial septal defect group who developed really severe pulmonary hypertension with inversed shunt and marked central cyanosis however and in whom operation was clearly contraindicated even according to current surgical standards (55) She died 9 years after the last catheterization at the age of 47 years in severe right cardiac decompensation. Autopsy showed a very large atrial septal defect and extreme organized and recent thrombotic occlusion of the pulmonary arteries It is well-known that "pulmonary embolism and thrombosis are important aggravating factors once pulmonary hypertension has developed in cardiac shunt lesions (30) There is "no evidence that they initiate the pul monary hypertension" (30) however

The tendencies expressed in fig 2 largely accord with earlier findings (18 30 36 55 64 80) Commonly there is a late development of cardiac failure as well as of pulmonary hypertension both in atrial septal defect (18 30 36 55 64 80) and many varieties of extracardiac shunts such as anomalous pul monary venous return (42) and systemic arteriovenous fistula (38 73) However large systemic arteriovenous fistula in children may lead to early cardiac failure (17) In atrial septal defect there is in general no correlation between the shunt volume (59 66) - or the anatomic defect size (80) - and the pulmonary arterial pressure Thus the pulmonary blood flow per se is rarely increased enough to call forth momentaneous pres sure increase and Wood concluded that many cases may continue to have large blood flow until 50-75 years of age when left ventricular failure will usually occur and that obliterative pulmonary hypertension protractedly develops but in a small number of cases (7 %) "in which a powerful hyperkinetic factor comes into being before complete post-natal involution and relaxation of the muscular pulmonary

of pulmonary hypertension (30) others that a certain minimal shunt size (1 cm/m^2 BSA) be required but no influence of the shunt size above this critical level (49) Wood found no case of ventricular septal defect with the Eisenmenger reaction and shunt size less than 1 cm^2 (80) and recently a satisfactory agreement between the pulmonary hypertension and the anatomic shunt size as measured during subsequent surgery was recorded (35) The pathophysiologic interpretations vary accordingly It has been suggested that there may be a congenital predisposition to pulmonary hypertension in certain patients due to weakness of the media of the lesser pulmonary arteries (30) and that inherent differences in the vascular bed may be responsible for a different reaction to similar hemodynamic stress (49) However other possible factors were recently thoroughly surveyed (64) such as increased pulmonary blood flow elevated left atrial pressure (see 55) increased pulmonary arterial oxygen saturation (54 76) systemic arterial unsaturation, and pulmonary vasoconstriction.

The above considerations may largely apply to persistent ductus arteriosus as well (14 21 25 28 29 40 45 55 57 71) in which, however there is also transmission of systemic arterial diastolic pressure to the pulmonary circulation and severe pulmonary hypertension may be established already during infancy with smaller anatomic shunt size than in ventricular septal defect therefore (80) There is also an extremely high mortality in the first year of life in persistent ductus arteriosus falling exponentially from the first week to the end of the year (14) However like in ventricula septal defect, pulmonary vascular obstruction rarely reaches significant degree until the second year of life (80) There may even be adult cases with severe pulmonary hypertension of hyperkinetic type with high shunt volume and relatively low pulmonary vascular resistance (71) In more complex intra cardiac shunt lesions of the types represented in the present material, direct transmission of the systemic pressure to the pulmonary circulation is of course often obligate

With this background it should be possible to interpret the findings regarding the majority of patients with persistent ductus arteriosus and in particular ventricular septal defect in the present material as predominantly relating to cases already having passed through the initial stages of the natural history of their pulmonary hypertension, according to two main patterns (fig 3); (a) those who have attained largely normal pulmonary arterial pressure remaining relatively well and normotensive thereafter (b) Those who have an established relapsing or persisting pulmonary hypertension, or in a few cases still are in the process of (re-)developing pulmonary hypertension. Extrapolation of the probable preceeding events might then allow the conclusions that in cases where severe established pulmonary hypertension was met with in early age there has either been no initial, post-natal decrease at all of the pulmonary arterial pressure or there has been a rapid relapse of pulmonary hypertension post natally In both situations the rapid establishment of severe pulmonary hypertension would seem to indicate pronounced provocing factors and would seem to bear a serious prognostic impli cation with short survival in most cases (fig 3) In patients where severe pulmonary hypertension was met with during adolescence or adulthood there may have been a more protracted redevelopment of pulmonary hypertension, perhaps according to the re-catheterization observations in some of the cases This might implicate less serious provocing factors and a correspondingly better prognosis with longer survival; in a few of the cases of ventricular septal defect in the material amounting 20 years or even more after the first catheterization (fig 3)

The hemodynamic features of pulmonary hypertension in shunt lesions are well-known and the findings in the present material need not be much discussed. Since evidence

has accumulated of increased left atrial pressure being a possible eliciting factor behind the development of pulmonary vascular obstruction in cardiac shunt defects (see 55) it was thought to be of interest however to graphically illustrate the relation between left atrial pressures as directly measured or as reflected in the PCV pressures and the pulmonary arterial pressures in the material (fig 4-7) Obviously there tends to be no satisfactory linear correlation between them *in the various disorder groups as a whole* Even though non-linear regression equations could be calculated as shown in the total material in fig 8 it is evident that in cases with significant degree of pulmonary hypertension precapillary pulmonary vascular obstruction with a high pressure gradient from the pulmonary arterial diastolic pressure to the PCV - left atrial pressure was the virtually sole mechanism encountered (fig 4-6) However in cases with normal or slightly increased pulmonary arterial pressures often exhibiting a large shunt volume slightly increased PCV pressures were not infrequent (fig 4 7) It is possible that the cases with significant pulmonary hypertension and predominantly characterized by established precapillary pulmonary vascular obstruction may have had developed this as a consequence of previously increased left atrial pressure which at the time of observation had normalized due to diminished pulmonary blood flow accompanying the pulmonary vascular obstruction. In general however the figures do not give evidence of a continuous transition between the two hemodynamic patterns as is for instance seen in mitral valvular disease where precapillary vascular obstruction rarely comes *into being until the left atrial-PCV* pressures have reached levels of 25 mm Hg or more (74)

Since the left atrial - PCV pressures are not directly illustrated in the PVR index (fig 9) this may give a less accurate expression of the above relations As implicated in the earlier discussion the PVR index tends to correlate rather well with pulmonary hypertension in shunt lesions however (fig 9) although high pulmonary blood flow may decrease its numerical value in some cases disproportionately to the magnitude of the pulmonary arterial diastolic pressure gradient against the PCV pressure (fig 8 9) The size of the pulmonary blood flow in turn, exhibits no good correlation to the degree of pulmonary hypertension (fig 10) which is well-known from a number of studies on large groups of patients with congenital heart disease *(see 84)*

The sex relations in the various disorder groups in the present series largely accord with other reports while an increasing predominance of females among the cases with pulmonary hypertension occasionally noted in earlier materials (29 30 45) could not be verified. One finding in the present report which is at variance with others is that the ventricular septal defect group was smaller than the atrial septal defect and persistent ductus arteriosus groups However as discussed earlier the material mainly consists of older children, adolescents and adults and includes only cases with the diagnosis confirmed by heart catheterization. Since spontaneous closure of ventricular septal defect may occur in as much as 30 % or more of all cases (16) and such patients would tend to escape the material, this might account for some of the discrepancy Similar selective factors also make the distribution of pulmonary hypertension in the various disorder groups hard to compare with other materials in particular those consisting mainly of infant cases The incidence does not seem to differ much however from that reported for instance by Wood (80) and Evans & Short (30)

SUMMARY

Occurrence pulmonary hemodynamical patterns natural history and prognostic implications in terms of crude mortality and survival of pulmonary hypertension in a material of congenital intracardiac and extracardiac shunt lesions are reported and briefly discussed in relation to the pertinent literature

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REFERENCES

1 Adams F H & Lind J : Physiologic studies on the cardiovascular status of normal newborn infants (with special reference to the ductus arteriosus) Pediatrics 19:431 1957

2. Arcilla, R.A. Agustsson, M.H. Bicoff J P Lynfield J Weinberg M.Jr Fell E.H. & Gasul B M.: Further observations on the natural history of isolated ventricular septal defects in infancy and childhood. Serial cardiac catheterization studies in 75 patientes Circulation 28:560 1963

3 Arcilla, R.A. Oh, W Lind, J & Gerner L.H. Pulmonary arterial pressures of newborn infants born with early and late clamping of the cord. Acta Pediat. Scand 55:305 1966

4 Badoud E : Über den Einfluss des Hirns auf dem Druck in der Lungenarterie. Arbeiten a. d. physiol. Laborat. d Würzburger Hochschule 3:237 1876

5 Baldwin, E deF Moore L.V & Noble R.P : The demonstration of ventricular septal defect by means of right heart catheterization. Amer Heart J 32.152 1946

6 Beutner A.: Über die Strom- und Druck-kräfte in der Arterie und Vena pulmonalis Zschr Rat Med N F 2:97 1852

7 Binak, K Regan, T J Christensen, R.C. & Hellems H.K.: Arteriovenous fistula: Hemodynamic effects of occlusion and exercise Amer Heart J 60-495 1960

8 Björck, G Salén, E F & Wiklund, Th.: Erfarenheter av hjärtkateterisering vid fall av medfödda hjärtfel. Svenska Läk. Tidn. 44:1045 1947

9 Bloomfield, D K : The natural history of ventricular septal defect in patients surviving infancy Circulation 29:914 1964

10 Braunwald, N.S Braunwald E & Morrow A.G : The effects of surgical abolition of left-to-right shunts on the pulmonary vascular dynamics of patients with pulmonary hypertension. Circulation 26.1270 1962

11 Broca, P : Des anéurysmes et de leur traitement, 1856 Cited by Posselt.

12 Brotmacker L. & Campbell M.: The natural history of ventricular septal defect. Brit Heart J 20:97 1958

13 Bühlmeyer K. Die pulmonale Hypertension bei angeborenen Herzfehlern im Kindesalter Bibl. paediat. p 85 S Karger Basel New York 1967

14 Campbell M. Natural history of persistent ductus arteriosus Brit Heart J 30-4 1968

15 Campbell, M.: Natural history of atrial septal defect. Brit. Heart J 32:820 1970

16 Campbell, M.: Natural history of ventricular septal defect. Brit. Heart J 33:246 1971

17 Childers R.W Ranniger K Rabinowitz M.: Intrahepatic arteriovenous fistula with pulmonary vascular obstruction in Osler-Rendu-Weber disease Amer J Med. 43:304 1967

18 Cohn, L.H. Morrow A.G & Braunwald E Operative treatment of atrial septal defect Clinical and haemodynamic assessments in 175 patients Brit. Heart J 29 725 1967

19 Cournand A. & Ranges H.A.: Catheterization of right auricle in man. Proc Soc Exp. Biol. 46 462 1941

20 Cournand, A. Lauson, H.D. Bloomfield, R.S. Breed, E S & de F Baldwin, E Recording of right heart pressures in man. Proc Soc. Exp Biol. 55 34 1944

21. Dammann, J F Jr Berthrong, M. & Bing R.J Reverse ductus; presentation of syndrome of patency of the ductus arteriosus with pulmonary hypertension and shunting of blood flow from pulmonary artery to aorta. Bull Johns Hopk. Hosp 92.128 1953

22 DeJesus J R.Jr Drake E H. & Gale H.H. Severe pulmonary hypertension secondary to congenital shunts in adult patients Circulation 24:916 1961

23. Dexter L. Haynes F W Burwell, C S Eppinger E C Sosman, M.C & Evans J M.: Studies of congenital heart disease III. Venous catheterization as a diagnostic aid in patent ductus arteriosus tetralogy of Fallot, ventricular septal defect and auricular septal defect. J Clin. Invest. 26.561 1947

24. Dexte L. Haynes F W & Smith, G T Ageing of the lung. p 194. Grune & Stratton, New York 1964

25 Ellis F H Jr Kirklin, J W Callahan, J A. & Wood E H. Patent ductus arteriosus with pulmonary hy pertension. J Thorac Surg. 31.268 1956

26 Emmanouilides G C Moss A.J Duffie E R.J & Adams F H.: Pulmonary arterial pressure changes in human newborns from birth to 3 days of age J Pediat 65:327 1964

27 Engle M.A. Ventricular septal defect in infancy Pediatrics 14:16 1954.

28 Eskildsen P Gøtzsche H. & Tybjaerg Hansen, A. Hjertekatheterisation ved medfødte hjertesygdomme Ugeskr Laeg. 111:497 1949

29 Espino-Vela, J Cardenas N. & Crux R.: Patent ductus arteriosus With special reference to patients with pulmonary hypertension. Circulation 38 Suppl. 5 45 1968

30 Evans W & Short D S Pulmonary hypertension in congenital heart disease Brit. Heart J 20:529 1958

31 Forssmann W : Ueber Kontrastdarstellung der Höhlen des lebenden rechten Herzens und der Lungenschlagader Munch. Med. Wschr 78:489 1931

32 Gomes M.R Bernatz P E & Dines D F Pulmonary arteriovenous fistulas Ann. Thorac Surg 7:582 1969

33 Gøtzsche H : Congenital heart disease The clinicoroentgenologic picture after the age of 2 years based upon about 200 cases with cardiac catheterization. Thesis Copenhagen, 1952

34. Hallidie-Smith K A.: The long-term results of closure of ventricular septal defect with pulmonary vascular disease Amer Heart J 76:591 1968

35 Hallidie-Smith, K.A. Hollman A. Cleland, W P Bentall H.H. & Goodwin, J F : Effects of surgical closure of ventricular septal defects upon pulmonary vascular disease Brit. Heart J 31.246 1969

36 H rbert W H Goyal P & Wadhwani B Early onset of pulmonary vascular obstruction with atrial septal defect Amer J Dis Child. 117;321 1969

37 Holman E : Contribution to cardiovascular physiology gleaned from

clinical and experimental observations of abnormal arteriovenous communications J Cardiovasc Surg 3 46 1962

38 Holman E Abnormal arteriovenous communications Great variability of effects with particular reference to delayed development of cardiac failure Circulation 32.1001 1965

39 Howitt G & Wade E G : Repeat catheterization in ventricular septal defect and pulmonary hypertension. Brit. Heart J 24-649 1962

40 Hultgren H. Selzer A. Purdy A. Holman, E & Gerbode F : Syndrome of patent ductus arteriosus with pulmonary hypertension. Circulation 8;15 1953

41 James L.S Rowe R.D : The pattern of response of pulmonary and systemic arterial pressures in newborn and older infants to short periods of hypoxia. J Pediat 51:5 1957

42 Kalke B R Carlson, R.G Ferlic R M. Sellers R.D & Lillehei C W : Partial anomalous pulmonary venous connections Amer J Cardiol. 20.91 1967

43 Kjellberg S.R Mannheimer E Rudhe U & Jonsson, B : Diagnosis of congenital heart disease p 119 Yearbook Publishers Inc Chicago Second edition, 1959

44 Kreysig F L. Die Krankheiten des Herzens p 603 11 Berlin 1816

45 Laustela E Tala P & Halttunen, P Patent ductus arteriosus with pulmonary hypertension. A report of 25 operated cases J Cardiovasc Surg 9.245 1968

46 Lichtheim L. Die Störungen des Lungenkreislaufes und ihr Einfluss auf die Blutdruck. Berlin 1876

47 Lillehei C W Anderson, R.C & W~ng Y Clinical and hemodynamic changes after closure of ventricular septal defects J Amer Med Ass 205:822 1968

48 Litten, M. Über Verengerungen im Stromgebiete der Lungenarterie Berl Klin. Wschr 19-425 1882

49 Lucas R.W Adams P Jr Anderson, R.C Meyne N G Lillehei C W & Varco R L. The natural history of isolated ventricular septal defect A serial physiologic study Circulation 24:1372 1961

50 Lynfield J Gasul B M. Arcilla, R & Luan, L.L.: The natural history of ventricular septal defects in infancy and childhood. Amer J Med 30 357 1961

51 Marey E J : Physiologie médical de la circulation du sang p 287 Paris 1863

52 Moulder P V Rams J J Dalcoff G R. & Cassels D E Surgical treatment of severe pulmonary hypertension. Dis Chest 51:39 1967

53 Nadas A.S Rudolph A.M Gross R E Pulmonary arterial hypertension in congenital heart disease Circulation 22.1041 1960

54 Nisell O L.: Action of oxygen and carbon dioxide on bronchioles and vessels of isolated perfused lungs Acta Physiol Scand. 21 (Suppl 73).1 1950

55 Oakley C M. & Goodwin J F : The current status of pulmonary embolism and pulmonary vascular disease in relation to pulmonary hypertension Progr Cardiovasc Dis 9-495 1967

56 Olin, C Rudhe U & Wallgren, G : Ventricular septal defect A study of its natural course in infancy and childhood. Cardiologia (Basel) 52:250 1968

57 Overbeck, W : Zum Verschluss des Ductus Botalli bei gleichzeitiger pulmonaler Hypertension. Thoraxchirurgie 14:534 1966

58 Park, C D Nicodemus H. Downes J J Miller W W & Waldhausen J A. Changes in pulmonary vascular resistance following closure of ventricular septal defects Circulation 39 (Suppl. I).193 1969

59 Petersson, P O Atrial septal defect of secundum type Acta Pediat. Scand. Suppl. 174 1967

60 Possolt A.: Die Erkrankungen der Lungenschlagader Ergebn. Allg Path. Path. Anat 13.298 1909

61 Reeve R. Selzer A. Popper R.W Leeds R.F & Gerbode F Reversibility of pulmonary hypertension following cardiac surgery Circulation 33 (Suppl. I):107 1966

62 Rowe R.D James L.S : The normal pulmonary arterial pressure during the first year of life J Pediat 51.1 1957

63 Rudolph, A.M. Drorbaugh, J E Auld P A. Rudolph, A.J Nadas A.S. Smith C A. & Hubbell, J P : Studies on the circulation in the neonatal period. The circulation in the respiratory distress syndrome Pediatrics 27:551 1961

64 Rudolph, A.M. & Nadas A.S : The pulmonary circulation and congenital heart disease Considerations of the role of the pulmonary circulation in certain systemic-pulmonary communications New Engl. J Med. 267:968 & 1022 1962.

65 Sandøe E Congenital isolated ventricular septal defect Haemodynamics clinical features and prognosis after the age of two years Thesis Copenhagen 1963

66 Saksena, F B & Aldridge H.E : Atrial septal defect in the older patient. A clinical and hemodynamic study in patients operated on after age 35 Circulation 42:1009 1970

67 Saling E : Neue Untersuchungsergebnisse über den Kreislauf des Kindes unmittelbar nach der Geburt. Arch. Gynäk. 194.287 1960

68 Sapru R.P Hutchinson, D C S. & Hall, J L Pulmonary hypertension in patients with pulmonary arteriovenous fistulae Brit. Heart. J 31:559 1969

69 Selzer A.: Defect of ventricular septum Arch. Intern. Med. 84 798 1949

70 Sterns L.P Indeglia R.A. & Lillehei C W : Clinical and hemodynamic results of ventricular septal defect closure in infancy Canad. J Surg 11 431 1968

71 Tikoff, G Echegaray H.M. Schmidt, A.M & Kuida, H.: Patent ductus arteriosus complicated by heart failure Amer J Med. 46 43 1969

72. Trell, E Johansson, B W Andrén, L. & Ohlsson, N -M.: The scimitar syndrome With particular reference to its pathogenesis Z Kreisl.-Forsch. 60-880 1971

73 Trell, E Johansson, B W Lindell F & Ripa, J Familial pulmonary hypertension and multiple abnormalities of large systemic arteries in Osler s disease To appear in Amer J Med

74. Trell, E Pulmonary hypertension in mitral valvular disease and heart constriction. With particular reference to the different hemodynamic patterns and notes on prognostic implications To appear in Cor et Vasa (Praha)

75 Tybjaerg Hansen A. Pressure measurement in human organism. Thesis Copenhagen 1949

76 van Bogaert, A. van der Henst H. van Genabeek A. & Vandael, J Tension artérielle pulmonaire et teneur en O_2 du sang de l artère pulmonaire: étude clinique et expérimentale Arch. Mal Coeur 46:961 1953

77 Wendt Bibl Laeger 1836 Cited by Posselt.

78 Werkö L. Mannheimer E & Lagerlöf, H. Hjärtkateterisering vid medfödda hjärtfel Svenska Läk -Tidn. 44.1893 1947

79 Wood, P Magidson, O & Wilson P A.O : Ventricular septal defect with a note on acyanotic Fallot s tetralogy Brit Heart J 16:387 1954

80 Wood P : Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Brit. Med J 2:701 & 755 1958

2 PULMONARY HYPERTENSION IN LUNG DISORDERS

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INTRODUCTION

Several articles during the last few years give thorough accounts of current pathologic and clinical (1 4 7 9 14-16 27 32 33 35 38 39 42 43 49 54 55) hemodynamical and pathophysiologic (2, 3 10 13 17 22 24 29 31 36 46-48 53) aspects of cor pulmonale - pulmonary hypertension in various dis orders of the lung and ventilation. In the present paper some findings regarding occurence hemodynamic patterns and prognostic implications of pulmonary hy pertension in a right heart catheterization material of pulmonary disorders will be briefly reported in relation to this and other pertinent recent literature

MATERIAL AND METHODS

During a 20-year period from the third quarter of 1948 126 patients with pulmonary parenchymatous disorders and potential or manifest ventilatory disturbances have been subjected to right heart catheterization performed according to routine techniques not further described here at the Heart Laboratory of Malmö General Hospital The heart catheterization findings have been studied in retrospect with regard to pulmonary arterial pressures

DIVISION OF PULMONARY HYPER TENSION

According to WHO s expert committee on cor pulmonale normal systolic pulmonary arterial pressures at rest are ≤ 25 mm Hg (13) Many authors (see 33 52) consider systolic pulmonary arterial pressures at rest exceeding 30 mm Hg to be raised. The physiologic variability of the pulmonary arterial systolic and mean pressures in normal individuals is rather small in most experimental situations not exceeding 10 mm Hg (52) The following division of pulmonary arterial systolic pressures measured at rest was applied in the present context:

Normal systolic pulmonary arterial pressure:	≤ 30 mm Hg
(Upper normal systolic pulmonary arterial pressure:	26-30 mm Hg)
Slightly elevated systolic pulmonary arterial pressure	31-40 mm Hg
Pulmonary hypertension.	≥ 41 mm Hg

Corresponding levels of the pulmonary arterial mean pressure are about 10 mm Hg lower (13) Upper normal limit of pulmonary capillary venous (PCV) pressure is considered to be 10(12) mm Hg (52)

FINDINGS

1 General findings in the material

Table 1 summarizes various disease groups in the material age and sex of patients and the distribution of recorded systolic arterial pressures within them Table 2 gives a representation of subsequent survival and mortality followed up to the autumn of 1971 The relation of pa tient ages to pulmonary arterial pressures is further illustrated in fig 1 In 88 of the cases arterial oxygen unsaturation values were obtained simultaneously with the heart catheterization and the relation between these and systolic pulmonary arterial pressures is given in fig 2 Fig 3 describes pulmonary arterial pressure increase on mild work (100 - 200 kpm/min or below) in a total of 40 patients investigated in this respect, and fig 4 the relation between pulmonary arterial pressures and pulmonary capillary venous pres sures as measured at rest in 52 of the cases In fig 5 this relation is analysed in terms of non-linear regression equations Fig 6 shows the relation of resting

Table 1

Disease	Total: Number ♀	Total: Number ♂	Total: Age m̄	Total: Age sd	Normal pulmonary arterial systolic pressure (≤ 20 mm Hg): Number ♀	Normal: Number ♂	Normal: Age m̄	Normal: Age sd	Sum Pulmonary hypertension (≥ 21 mm Hg): Number ♀	Hypertension: Number ♂	Hypertension: Age m̄	Hypertension: Age sd
I Chronic obstructive pulmonary disease	14	39	50 3	12 0	10	30	49 0	12.3	4	9	54 8	9 9
II Parenchymal diseases												
) Cancer	9	16	57 4	10 7	9	10	55 0	12 2	0	6	61 8	6 7
b) TBC	6	13	42.8	12.4	5	12	41 4	13 3	1	1	62 6	(13 4)
c) Others	1	10	44 6	14 0	1	10	44 6	14 0	0	0		
Sum II a–c	7	39	48 4	14 1	6	32	46 0	14 1	1	7	63 3	8 7
III Pulmonary fibrosis	2	3	39 2	22 8	1	0	6		2	3	47 6	17 2
IV Ventilatory disturbances												
) Pes excavatum	4	7	21.0	10 4	4	6	23 1	11 0	0	1	22.	
b) Pleural diseases	2	6	58 9	9 9	0	4	62 8	10 8	2	2	59	6.6
) Obesity	1	2	40 7	16.3	1	0	29		0	2	56 5	(9 7)
Sum IV b	7	16	36 2	18 7	6	10	31 4	16 8	2	5	52 7	14 4
Sum I II III IV	30	96	47 0	16 2	22	72	44 8	18 4	8	24	54 4	11 7

Table 1 (Abbreviations m̄ mean, sd standard deviation) Sex and age (years) of patients and various diseases in the material Chronic obstructive pulmonary disease" includes chronic bronchitis emphysema and bronchial asthma. In "parenchymal diseases" cancer" designates cases primarily investigated on behalf of pulmonary malignancy malignant thymoma in one case bronchogenic carcinoma in the others. Group IIc includes miscellaneous conditions such as sarcoidosis and anthracosis and cases investigated on behalf of suspected pulmonary parenchymatous disease The table gives numbe of females and males in the various groups and pulmonary arterial pressure levels while for matters of brevity age of patients includes both sexes. Also f matters of brevity ge range is not represented. The table i divided into three sections; to the left ll cases withi the various disease groups re summed up in the middle those with normal pulmonary rterial systolic pressure re compared with the sum of patients with various degrees of pulmonary rterial pressure increase and to the right the latter patients re subdivided in consecutive level of pulmonary hypertension.

	Slightly elevated PA systolic pressure (31 – 40 mm Hg)				Moderate pulmonary hypertension (41 – 50 mm Hg)				Pronounced pulm. hypertension (52 – 60 mm Hg)				Severe pulmonary hypertension (≥ 61 mm Hg)					
	Number		Age		Number		Age		Number		Age		Number		Age		Pulmonary arterial systolic pressure	
	♀	♂	m	sd	♀	♂	m	sd	♀	♂	m	sd	♀	♂	m	sd	m	range
	4	5	33,8	11,1	0	4	50,0	5,3	0	0			0	0				
	9	4	64,3	3,6	0	2	34,0	[illegible]	0	0			0	0				
	2	2	52,5	(13,0)	0	0			0	0			0	0				
	0	0			0	0			0	0			0	0				
	1	5	50,3	8,8	6	2	56	(9,9)	0	0			0	0				
	0	0			0	1	47		1	0	72,0		0	2	38	(8,3)	90	83–93
	0	0			0	1	22,		0	0			0	0				
	2	2	63	6,8	0	0			0	0			0	0				
	0	1	58		0	1	63		0	0			0	0				
	3	3	58,4	8,8	0	2	30,5	(22,3)	0	0			0	0				
	7	15	56,4	9,8	0	0	53,4	13,6	1	0	71		0	2	38	(5,5)	90	85–96

pulmonary arterial pressures to cardiac output (fig 6a – b) and to PVR-indexes (fig 6c) and fig 7 the elevations of cardiac output and pulmonary artery mean pressure on mild work in the patients investigated in this respect. In fig 8 increases of PCV pressures on exercise in 17 patients are represented and in fig 9 are compared with increases of cardiac output in 7 of them.

Briefly commenting the tables it may be noted that pulmonary arterial pressures at rest were normal in the majority of cases in the material (15 of the patients with chronic obstructive pulmonary disease 14 with pulmonary parenchymatous disease and one each of the pulmonary fibrosis and pes excavatum cases had upper normal pulmonary arterial systolic pressures however) Slightly increased pressures were not infrequent in the chronic obstructive and pulmonary parenchymatous disease groups while clear-cut pulmonary hypertension was uncommon, except for in the pulmonary fibrosis group (table 1) In this three patients had severe pulmonary hypertension (systolic pulmonary arterial pressures 80 83 and 95 mm Hg) one had moderate pulmonary hypertension (63 mm Hg) and one had upper normal systolic pulmonary arterial pressure (28 mm Hg) In the chronic obstructive lung disease group there was a slight correlation between the age of the patients and the level of pulmonary arterial pressures (table 2 fig 1a) which was not obvious in the parenchymatous disease group as a whole (fig 1b) although the cases with the highest pulmonary arterial pressures tended to be found among the more advanced ages (table 2 fig 1b) The other groups were too small and heterogeneous to allow a certain tendency to appear Regarding the relation between pulmonary artery pressure levels and subsequent survival and mortality table 2 shows that prognostical implications were more pessimistic in patients with pulmonary hypertension also if the cases primarily investigated on behalf of pulmonary malignancy are excluded. Arterial oxygen unsaturation was common in the investi-

Table 3

Diseases (the same groups as in table)	Total: Surviving nr	Total: Surviving time	Total: Dead nr	Total: Dead time	Lost for follow-up	Normal A systolic pressure (≤ 30 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up	Sum Pulmonary hypertension (≥ 31 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up	Slightly elevated PA systolic pressure (31–40 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up	Moderate pulmonary hypertension (41–60 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up	Pronounced pulmonary hypertension (61–80 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up	Severe pulmonary hypertension (≥ 81 mm Hg): Surviving nr	Surviving time	Dead nr	Dead time	Lost for follow-up
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]		[illegible]		[illegible]	[illegible]		[illegible]			[illegible]		[illegible]			[illegible]		[illegible]	[illegible]	[illegible]							[illegible]		
a)			[illegible]		[illegible]		[illegible]		[illegible]	[illegible]				[illegible]	[illegible]				[illegible]				[illegible]	[illegible]				[illegible]							
b)		[illegible]		[illegible]	[illegible]	[illegible]			[illegible]	[illegible]		[illegible]			[illegible]		[illegible]			[illegible]											[illegible]				[illegible]
c)	[illegible]	[illegible]				[illegible]	[illegible]									[illegible]										[illegible]									[illegible]
Sum a–c	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]		[illegible]			[illegible]		[illegible]	[illegible]	[illegible]	[illegible]		[illegible]					[illegible]	[illegible]										
III			[illegible]					[illegible]						[illegible]									[illegible]	[illegible]				[illegible]	[illegible]				[illegible]	[illegible]	[illegible]
IV																																			
a)		[illegible]		[illegible]		[illegible]	[illegible]			[illegible]				[illegible]										[illegible]											
b)				[illegible]			[illegible]							[illegible]			[illegible]	[illegible]	[illegible]				[illegible]							[illegible]					
c)		[illegible]		[illegible]			[illegible]				[illegible]	[illegible]		[illegible]			[illegible]						[illegible]	[illegible]											
Sum IV a–c		[illegible]		[illegible]		[illegible]	[illegible]					[illegible]		[illegible]		[illegible]	[illegible]		[illegible]					[illegible]	[illegible]	[illegible]				[illegible]					
Sum I–IV	[illegible]		[illegible]	[illegible]		[illegible]		[illegible]			[illegible]		[illegible]	[illegible]			[illegible]		[illegible]		[illegible]	[illegible]		[illegible]	[illegible]	[illegible]		[illegible]					[illegible]	[illegible]	[illegible]
Sum I–IV minus Cancer	[illegible]		[illegible]	[illegible]		[illegible]		[illegible]	[illegible]		[illegible]		[illegible]	[illegible]			[illegible]		[illegible]			[illegible]	[illegible]	[illegible]					[illegible]				[illegible]	[illegible]	

Table 2: (*Abbreviations: nr number of cases* Time stands for the mean duration of survival from the time of catheterization or the mean time until death after the time of catheterization while range and standard deviation are not given)
In the table results of follow up investigation regarding survival and mortality of the cases in the material up to the autumn of 1971 are *represented* For matters of brevity it is not separated in this table between females and males The table contains an additional horizontal column representing the sum of cases in the material minus those primarily investigated on behalf of pulmonary malignancy Otherwise the table contains the same groups as table 1

PULMONARY ARTERIAL SYSTOLIC PRESSURE (mm Hg)

60

40

20

n = 53
r = 0 36
c = 13 43
m = 0 21

20 40 60 80 100
AGE (YEAR)

Fig 1a

PULMONARY ARTERIAL SYSTOLIC PRESSURE (mm Hg)

40

20

n = 46
r = 0 17
c = 21 11
m = 0.08

20 40 60 80
AGE (YEAR)

Fig 1b

Fig 1 (Abbreviations in this and following illustrations·
n = number of observations
r = correlation coefficient,
c = intercept on y coordinate
m = slope of regression line)
Relation of resting pulmonary arterial systolic pressure to age of patients
a. Chronic obstructive pulmonary disease group ($p < 0\ 01$)
b Pulmonary parenchymatous disease group (no significance)

gated cases (fig 2a – f) It exhibited a varying degree of correlation with recorded pulmonary artery pressures within the chronic obstructive lung disease (fig 2a) pulmonary fibrosis (fig 2c) and ventilatory disturbance groups (fig 2d) and in the material as a whole (fig 2f) On mild short-term exercise (100 200 kpm/min or less) pulmonary arterial pressure increase regularly occurred in investigated cases and was of definitively pathologic degree in not so few (fig 3) Interestingly as shown in figures 8 and 9 this was often accompanied by an increase f the PCV pressure which was uppe normal or increased in a few cases also at rest (fig 4 a g) However a pulmonary arterial diastolic pressure gradient against the PCV pressure was a regular hamodynamic feature (fig 4c f) apart from in the cases of pes excavatum where PCV pressures and

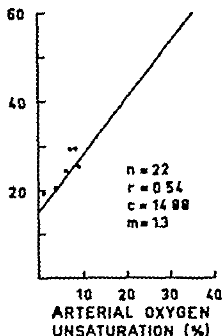


Fig 2a

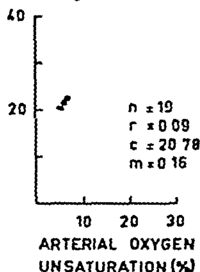


Fig 2b

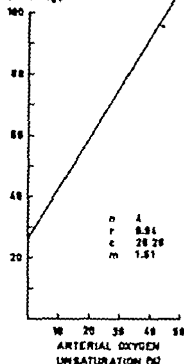


Fig 2c

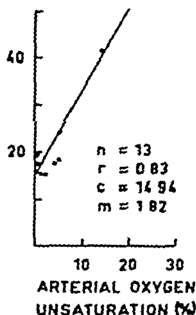


Fig 2d



Fig 2a

Fig 2 Relation of resting pulmonary arterial systolic pressures to arterial oxygen unsaturation.
a Chronic obstructive pulmonary disease group ($p < 0.01$)
b Pulmonary parenchymatous disease group (no significance)
c Pulmonary fibrosis ($p < 0.01$)
d Ventilatory disturbances ($p < 0.001$) Sum a–d ($p < 0.001$)

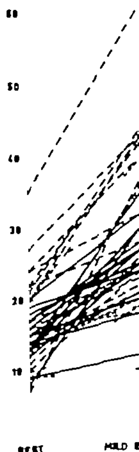


Fig 3 (– – – – – chronic obstructive pulmonary disease ——— = pulmonary parenchymatous disease – – = ventilatory disturbances) Mean pulmonary art rial pressure increase on mild ex rcise (n 40)

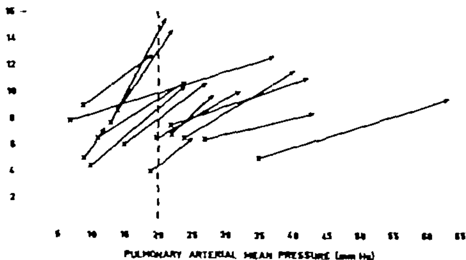


Fig 7 Increases of cardiac output and pulmonary arterial mean pressures on mild exercise Total material n = 15

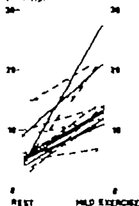


Fig 8 (Symbols the same as in fig 3) Increases of PCV mean pressures on mild exercise (n 17)

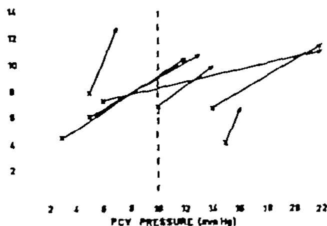


Fig 9 Increases of cardiac output and PCV pressures on mild exercise Total material n = 7

1. Interesting cases within the material

The material contains a comparatively large series of a type of thorax deformity otherwise infrequently studied with regard to pulmonary hemodynamics namely eleven cases of pes excavatum (table 1) Normal pulmonary hemodynamic findings were recorded in 9 of them. One case a 28-year old woman had normal pulmonary arterial pressures (24/14 mean 19 mm Hg) but had increased PCV (mean 15 mm Hg) and right atrial (mean 10 mm Hg) pressures as signs of heart constriction, and one case a male aged 22 years with very pronounced pes excavatum, had a history of exertional dyspnea since 12 years intermittent ankle oedema and other clinical features of cor pulmonale At catheterization, pulmonary hypertension with pronounced breathing-variations (13) was noted the pulmonary arterial systolic pressures during expiration being 45-60 mm Hg and during deep inspiration lowering to near 30 mm Hg. He died 9 days after the heart catheterization in respiratory and right cardiac failure. Autopsy findings were severe pes excavatum "with secondary pulmonary fibrosis and right ventricular hypertrophy

In the pulmonary malignancy group one case has been reported in detail elsewhere (50) He was a 49-year-old man, with advanced malignant thymoma which infiltrated in the left pleura and pulmonary parenchyma into the pericardium and myocardium, and compressed the superior vena cava the left main and upper lobe pulmonary arteries and the left pulmonary veins He had moderate pulmonary hypertension with pulmonary arterial systoli pressure of 46 mm Hg which could be possibly related to many of the above complications (50) Four cases of bronchial cance had slightly increased pulmonary arterial pressures and one had moderate pulmonary hypertension (45 mm Hg) All of them were over 60 years of age protracted smokers (44) and had an ea lier history of airway symptoms As showed by Jezek (33) pulmonary arterial pressures tend to be higher in cases of bronchial cancer with an earlier history of repeated or chronic bronchitis than in cases without other airway symptomatology

Severe pulmonary hypertension may develop in pleural disease (14) In the present material slightly elevated pressures (31-36 mm Hg) were recorded in one case of pleural adherences one case of exsudative pleuritis and two cases of rapidly growing near terminal pleural mesothelioma.

Pulmonary fibrosis is a heterogeneous disease group It is well-known that diseases belonging to it tend to give rise to the most pronounced pulmonary hypertension among disorders of the lung (16) In the present material really severe pulmonary hypertension was encountered only within the pulmonary fibrosis cases Two of them have been reported earlier One a 39-year-old- man had fibrosing alveolitis (51) He had pronounced pulmonary hypertension (85/37 mean 49 mm Hg) but only moderately increased pulmonary vascular resistance (mean PCV pressure 15 mm Hg cardiac output 7 8 l/min and pulmonary vascular resistance index 4 4 units) The second a 47-year-old man had an unique genetically determined hemoglobinopathy and pulmonary fibrosis (6) and his pulmonary artery pressures were 55/27 mean 39 mm Hg Further cases of pulmonary fibrosis in the material were a 71-year-old woman whose pulmonary artery pressures were 80/33 mean 48 mm Hg and mean PCV pressure 4 mm Hg and a 42-year-old man with a history most suggestive of an extrinsic allergic alveolitis" (45) type of disorder He was born in 1927 and his earlier history was unremarkable Since 1960-61 he had lowly increasing exertional dyspnea peripheral cyanosis and finger lubbing and since 1963 repeated bouts of dry irritative cough. He was first heart catheterized in 1967 when pulmonary arterial pressures were 42/20 mean 27 mm Hg mean PCV pressure 6 mm Hg cardiac output 4 1

in the present series (fig 7) cardiac output has not been shown to increase abnormally on work in the majority of cases loss of the normal capillary reserve volume may magnify the effects of exertional flow elevation (42) Further vasoconstriction due to impaired blood gases (25 30 34) and influence of intrathoracic and alveolar gas pressures (22 30 53) accentuated by exertional dyspnea (53) may both operate in the direction of increased pulmonary vascular resistance However like in the present material (fig 8-9) elevation of the PCV pressure often occurs as well (30 27) This would implicate alveolar gas compression or perhaps increased broncho-pulmonary arterial collateral supply (28 37) distal to the site of wedging (37) Instead increased left ventricular end-diastolic pressure behind the PCV pressure elevation has been proposed (37) It has been increasingly appreciated that cor pulmonale is a disease of the whole heart" (8) and that left ventricular failure may occur in chronic pulmonary disease (46) In such patients there was mild to moderate pulmonary hypertension and the pulmonary arterial wedge pressures and left atrial pressures were increased in some of the cases even exceeding the pulmonary arterial diastolic pressures (46) This is at variance with the statement that a pulmonary arterial diastolic gradient against the PCV pressure is regular in chronic pulmonary disease (25) The latter tendency with few exceptions appears in the present material (fig 4-5) and is compatible with an element of increased pulmonary vascular resistance (25) (fig 6c) However a few cases already at rest and not so few during mild effort had increased PCV pressures too (figures 4 8 9) As implicated above such findings are difficult to interpret but are not inconsistent with the concept of left ventricular dysfunction, although superimposed by pulmonary vascular factors possibly contributing to the development of pulmonary hypertension in a proportion of the patients with chronic lung disease (46) The ages of the patients may offer an additional influence since it has been shown that PCV pressures obtained on exercise are raised in healthy old men (61-63 years) (20 21) None of the patients studied at exertion in the present series was older than 65 years however Several plausible mechanisms of left heart failure in chronic pulmonary disease have been thoroughly discussed by Rao et al. (46)

SUMMARY

The occurrence of pulmonary hypertension within a material of chronic pulmonary diseases and of potential or manifest ventilatory disturbance is briefly reported. Included in the material are some interesting single cases and a comparatively large series of a thorax deformity possibly interfering with respiratory function and otherwise little studied with regard to pulmonary hemodynamics namely pes excavatum One of the patients in the latter group had cor pulmonale and another had signs of cardiac constriction. Severe pulmonary hypertension was observed only among the pulmonary fibrosis cases while pulmonary artery pressures at rest were normal or slightly increased in the majority of cases with chronic obstructive and pulmonary parenchymatous diseases Interpretation of this and some parameters relating to the pulmonary hemodynamics in the material are discussed in relation to pertinent, recent literature

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REFERENCES

1 Abraham A.S Cole, R.B and Bishop J M.: Reversal of pulmonary hypertension by prolonged oxygen administration to patients with chronic bronchitis Circulat. Res 23:147 1968

2. Abraham A.S Cole R.B Green, I D Hedworth-Whitty R.B Clarke S W and Bishop J N Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studied by serial observations during recovery Circulat Res 24.51 1969

3 Abraham A.S Hedworth-Whitty R B and Bishop J M.: Effects of acute hypoxia and hypervolaemia singly and together upon the pulmonary circulation in patients with chronic bronchitis Clin. Sci. 33 371 1967

4 Addington, W W Pf ff r S H. and Gaensler E A. Obesity and alveolar hypoventilation. Respiration 26:214 1969

5 Altschule M.D Cor pulmonale- A disease of the whole heart Dis Chest 41:398 1962

6 Berglund, S In preparation.

7 Bignon, J Khoury F Even, P Andre J and Broust, C M rphometric study in chronic obstructive bronchopulmonary disease Pathologic clinical and physiologic correlations *Amer Rev Resp Dis* 99-669 1969

8 Bland J W Edwards F K and Brinsfield, D : Pulmonary hypertension and congestive heart failure in children with chronic upper airway obstruction. Amer J Cardiol. 23:830 1969

9 Block A.J Wexler J and McDonnel E J : Cardiopulmonary failure of the hunchback A possible therapeutic approach J Amer Med. Ass 212:1520 1970

10 Bristow J D Morris J F and Kloster F E : Hemodynamics of cor pulmonale, Progr Cardiovasc Dis 9 239 1966

11 Cournand, A. Some aspects of the pulmonary circulation in normal man and in chronic cardio-pulmonary diseases Circulation 2:641 1950

12 Daly J J : Venoarterial shunting in obstructive pulmonary disease New Engl J Med 278 952 1968

13 Dankmeijer J Herles F Ibrahim M. Reid D D Richards D W Stuart Harris C H Taquini A.C and Werkö L.: Chronic cor pulmonale Report of an expert committee Circulation 27:594 1963

14 Degenring F H Radeck, R and Uhse H.G : De Pulmonalarteriendruck bei Pleurapunktion. Ein Bericht übe sieben Fälle mit Pleura erguss Z Kreisl -Forsch 59:524 1970

15 Doll E Kuhlo W Steim H and Keul J : Zur Genese des Cor pul monale beim Pickwick Syndrom. Dtsch. Med. Wschr 42 2361 1968

16 Edwards J E : Pulmonary hypertension of cardiac and pulmonary origins Pathologic aspects Progr *Cardiovasc Dis 9:206 1966*

17 Eichenholz A. Blumentals A.S and Walker F E The pattern of compensatory response to hronic hypercapnia in patients with chronic obstructive pulmonary disease. J Lab. Clin. Med. 68.265 1966

53 Weitzenblum E Vandevenne A. Roeslin N Hirth C and Oudet, P : Fréquence et modalités de l hypertension artérielle pulmonaire d effort dans les bronchopathies chroniques J Franç Méd, Chir Thor 24.263 1970

54 Wentworth P Gough, J and Wentworth J E Pulmonary changes and cor pulmonale in *mucoviscidosis* Thorax 23:582 1968

55 Williams M.H Jr and Shim C S : Ventilatory failure Etiology and clinical forms Amer J Med. 48:477 1970

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Shock Complicating Acute Myocardial Infarction

A clinical hemodynamic and therapeutic study

By Olof Nyquist

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To
Whom it may concern

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Stockholm Sweden.

SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION

A clinical hemodynamic and therapeutic study

by

OLOF NYQUIST

STOCKHOLM 1972

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Contents

Introduction

The hospital mortality of acute myocardial infarction, AMI, has decreased with the introduction of coronary care units, CCU mainly due to the improved treatment of arrhythmias. However the incidence and mortality of shock complicating AMI have remained virtually unchanged and shock nowadays accounts for a major proportion of the hospital mortality of AMI. For further reduction of the present mortality figures in AMI, advances must obviously be aimed at the problems concerning this complication.

There is therefore a need for more information about the clinical and hemodynamic features in shock secondary to AMI and for further clinical and hemodynamic evaluation of modern shock therapy. Early detection and treatment of arrhythmias in AMI has given promising results, and a corresponding approach to the shock problem may similarly be of value. In this context a prerequisite is a shock predictive index.

Accordingly the aim of the present investigation was:

Part I to study the incidence, clinical features, mortality and some autopsy findings in shock and hypotension in a large consecutive series of patients with AMI admitted to a CCU.

Part II to study the central hemodynamics in patients with shock complicating AMI.

Part III to study the clinical and hemodynamic effects of volume loading in the same patients.

Part IV to study the clinical and hemodynamic effects of intra-aortic balloon pumping in those patients not responding to volume loading.

Part V to find a shock predictive index on the basis of clinical findings on admission in a retrospective CCU material and to test this index prospectively during one year.

The value of hemodynamic studies has to be weighed against the risks of inflicting harm on the patients. However, the very high mortality in patients with shock in AMI necessitates close observation by monitoring of central hemodynamics during treatment with such methods as volume loading and assisted circulation. This opinion has been supported by the Committee of Ethics at Karolinska Institutet, whose advice had been sought.

PART I
Clinical features

It has been shown that the hospital mortality of AMI is lowered by treatment in a CCU (Hofvendahl 1971 and Christiansen et al. 1971). Following the improvement in prevention and treatment of arrhythmias (Lown et al. 1967a and 1967b and Killip and Kimball 1968), cardiogenic shock has become the leading cause of death in AMI (Swan et al. 1970 and Lundman et al. 1972). The incidence and mortality of shock have remained virtually unchanged (Killip and Kimball 1967 Lawrie et al. 1967 Lown et al. 1967a, Wallace et al. 1967 Meltzer 1968 Bloomfield et al. 1970, Scheidt et al. 1970 Hofvendahl 1971 and Sloman and Hunt 1971). Recently a lower incidence has been reported in association with use of mobile CCUs (Adgey et al. 1971).

Autopsy studies on patients who have died in shock (Harnarayan et al. 1970 Page et al. 1971 and Scheidt et al. 1972) generally report on massive myocardial damage. However there are three autopsy findings that encourage to further therapeutic trials. First, there are some few infarcts that are small (Harnarayan et al. 1970). Secondly the infarcts consistently show marginal extensions and thirdly there are frequently areas of necrosis and hemorrhages scattered throughout the myocardium, which may have developed secondary to the hypotensive state (Page et al. 1971). These latter two findings especially encourage attempts with prophylactic treatment

The purpose f this part of the present investigation was to determin the incidence, clinical features, mortality and some autopsy findings in shock and hypotension due to AMI The study was performed on a consecutive series of patients admitted to the CCU f Serafimerlasarettet in Stockholm.

MATERIAL AND METHODS

All patients admitted to this CCU from January 1 1968 to January 1 1971 were included. A standarized data chart and prospectively defined shock criteria were used for the whole material. Organization of the CCU general care, treatment of complications, investigations and after-care will be described briefly A more detailed account has been presented previously (Björck et al. 1969).

ADMISSION CRITERIA

Patients admitted to the Casualty Department of Serafimerlasarettet who fulfilled at least one of the following criteria were immediately transferred to the CCU The admission criteria were:

1 central chest pain lasting for more than 15 minutes beginning within the last 48 hours
2 frank pulmonary oedema without previously known valvular lesion uremia or intoxication
3 shock not due to acute intoxication or bleeding
4 syncope with electrocardiographic evidence of AMI
5 intractable angina pectoris.

The last two criteria were added on September 18 1968.

ORGANIZATION OF THE CCU AND GENERAL CARE

During the first 9 months of the 3 year period the patients were treated in a temporary unit consisting of 3 single rooms and thereafter in a 7 single room unit. During the earlier period, only about half of the patients fulfilling the above criteria for admission could be received at the CCU The principle for selection was the availability of a bed in the CCU at the moment of call from the Casualty Department. All patients fulfilling the admission criteria could be received in the 7 room unit.

The patients ECGs were monitored, by use of precordial electrodes, on a bedside oscilloscope and on a slave oscilloscope placed centrally There were no fluoroscopic facilities in the CCU and transvenous pacemaker electrodes were therefore inserted in another department.

All patients were clinically examined on admission and thereafter at least three times daily Heart rate, respiratory rate and blood pressure were routinely measured by the nurses on admission and then every hour Findings, including arrhythmias were noted on special time marked sheets and summarized every 1 hours in a data chart.

DISCHARGE

The duration of stay in the CCU was set according to defined criteria and terminated irrespective of time of day The patients were treated in the CCU for at least 48 hours in the 3 bed unit and for at least 24 hours in the 7 bed unit. Following sinus bradycardia, A V block II, frequent multifocal, coupled or early ventricular ectopic beats, hypotension and shock, 4 hours without these complications were to have passed before discharge The corresponding free interval following ventricular fibrillation, ventricular tachycardia (defined as three successive ventricular ectopic beats or more) or complete heart block, was 48 hours.

In uncomplicated cases, patients were mobilized progressively with the aid of a physiotherapist toward the end of the first week or beginning of the second, and then encouraged to become increasingly physically active. The patients were usually discharged towards the end of the third week.

DEFINITIONS AND TREATMENT

General treatment

Humidified oxygen, 4 lit. per min., was given by mask or nasopharyngeal catheter to all patients, as well as a slow 5.5 per cent glucose intravenous drip Any previous drug treatment was usually discontinued on admission. Severe pain was treated with oxycodone, pethidine or pentazocine. Dicumarol as given routinely unless contraindicated. Heparine was not given.

Treatment of arrhythmias

Supraventricular bradycardia was treated with atropine sulphate or methyl scopolamine intravenously In cases with hypotension, shock or cerebral symptoms and bradycardia not responding to this therapy endocardial pacing was instituted.

Atrial fibrillation or flutter with heart rates over 120 per min. was treated with 0.25—0.38 mg ouabain and 20 mg frusemide intravenously If coexisting severe hemodynamic dysfunction such as hypotension, shock, anginal pains or frank pulmonary oedema was present, DC electroconversion was immediately performed.

Nodal rhythm with or without A V dissociation was treated with digitalis withdrawal and atropine sulphate or methyl scopolamine. Nodal tachycardia in association with signs of severe hemodynamic dysfunction was immediately treated with DC electroconversion.

A V block I and II was managed by withdrawal of digitalis and administration of atropine sulphate or methyl scopolamine intravenously Complete heart block was treated with an on demand endocardial pacing system, which was kept going until 48 hours had elapsed after restored supraventricular rhythm.

Ventricular ectopic beats and ventricular tachycardia were treated with lignocaine intravenously After a bolus dose of 50 to 100 mg, a constant infusion of 1 or mg per min. followed. Other antiarrhythmic drugs including procaine amide, diphenylhydantoin quinidine and beta-adrenergic blocking agents and combinations of these were given if lignocaine therapy failed. Persistent ventricular tachycardia was treated with DC electroconversion. Immediate defibrillation was performed in patients with ventricular fibrillation.

Treatment of heart failure

Heart failure as defined by the presence of more than a few scattered basal rales, was primarily treated with 10 to 40 mg frusemide intravenously Patients with frank pulmonary oedema were also given digitalis, oxycodone theophyllamine and increased amounts of oxygen. A sitting position was

adopted, and occasionally venous occlusion of the extremities as well as manually assisted ventilation were employed.

Treatment of hypotension

Hypotension, defined as a systolic blood pressure of 90 mm Hg or below but unaccompained by clinical signs of shock, was treated with atropine sulphate or methyl scopolamine intravenously when the heart rate was below 80 per minute. This was supplemented by rapid intravenous infusion of 5.5 per cent glucose (see below treatment of shock)

Treatment of shock

Definition of shock. Shock was defined as a palpatory systolic blood pressure below 90 mm Hg for more than half an hour in association with at least three of the following findings.

1 signs of reduced cerebral circulation such as mental confusion or unconsciousness
2. signs of reduced peripheral circulation such as cold skin
3 signs of reduced renal circulation with a urine flow less than 20 ml per hour
4. peripheral or general cyanosis
5 metabolic acidosis.

Patients fulfilling the above criteria of shock were treated according to the following stepwise policy

1 a slightly head down posture (if not in frank pulmonary oedema)
2 oxygen 10 lit. per min. by mask or nasopharyngeal catheter
3 methyl scopolamine or atropine sulphate intravenously when the heart rate was below 80 per min
4 120 mE ((0) ml) sodium bicarbonate intra nusly The ter further administration ac d ng t a id has alysis of arterial blood
5 300 ml 5.5 per ent lu ose by rapid infusion if no frank p lmon ar oedema or signs of elevated central enou essure were present
6 isoprenaline ab ut 3 m gram per min., in a onstant drip.

INVESTIGATIONS

Routine ECGs including leads I II III aVR aVL, aVF CR_4R, CR_1 CR_2, CR_4, CR_5 and CR_7 were taken with an ink jet recorder on admission and every morning during the CCU stay Bedside chest X-ray and arterial blood for gas analysis was taken on special indications. Serum enzymes were determined on admission and every morning during the CCU stay The following enzymes were routinely determined (reagents from KABI AB, Stockholm, Sweden): serum aspartate aminotransferase (GOT) serum alanine aminotransferase (GPT) lactic dehydrogenase (LDH) and its isoenzymes LD_1 and LD_2 as alfahydroxybutyrate dehydrogenase (HBD).

Diagnostic criteria

On the basis of the daily ECG and serum enzyme determinations the patients fulfilling any of the admission criteria received either of the following diagnoses: acute myocardial infarction suspected infarction or nonproven infarction.

The criteria for the diagnosis of acute myocardial infarction in these patients have been the fulfilment of a, b or c below in addition to the admission criteria.

a) appearance of a pathologic Q-wawe, and/or appearance or disappearance of a localized ST elevation followed by a T inversion in 2 or more of the 12 leads.
b) 2 GOT-values of 40 units or more and with a maximum about 24 hours after onset of symptoms in combination with lower GPT values with a maximum after about 36 hours and/or HBD-values exceeding 75 per cent of corresponding LDH values higher than 40 units, with a maximum about 60 hours after the onset of symptoms, or combination of one GOT GPT pair and one HBD LDH pair elevated as stated above.
c) findings at autopsy of myocardial necrosis of an age corresponding to the onset of symptoms.

INFARCTION SITE

The sites of infarction were localized from changes observed in the daily 12 lead ECG They were

interpreted as being either anterior anterolateral, lateral, inferior inferolateral, anteroinferior or combined anteroinferolateral.

The ECG criteria for anterior infarction were changes occurring in leads CR ı, lateral in leads I, aVL and CR₇ and inferior in leads II, III and aVF

AUTOPSY

Autopsy included a rough estimation by the pathologist of per cent of the left ventricular myocardium which was infarcted, as well as of the age of the infarct

DATA REGISTRATION

The findings for each patient during the CCU stay were directly recorded into specially constructed registration charts in numerical form (Lundman et al 1968). The charts were supplemented with information f om the after-care period and controlled at two instances by physicians. The data were evaluated by means of a computer

STATISTICAL METHODS

Conventional methods have been used for the calculation of the arithmetic mean, standard deviation (S.D) and correlation coefficients (r). Age has been calculated from 10 years class means. Significance of differences between mean values were tested by Student's t-test. The Chi-square test with Yates correction was used for testing the significance of differences of relative numbers. Degrees of significance were tested at the 5 1 and 0.1 per cent level. The methodological error obtained from duplicate estimations was calculated according to the formula $\sqrt{\frac{\Sigma d^2}{2n}}$ where d is the difference between the paired estimations and n the number of estimations.

RESULTS

During the period of study there were 1780 admissions to the CCU Of these 693 (39 per cent) fulfilled the criteria for a diagnosis of AMI. In the following text each of these admissions will be referred to as a different patient. There were 445 men (64 per cent) and 48 women (36 per cent). The mean age for all patients was 65 years. 43 per cent were admitted within 3 hours after onset of symptoms, 65 per cent within 6 hours and 78 per cent within 12 hours. The mean CCU stay was 53 hours and the mean hospital stay 19 days.

Of the 693 patients with AMI 85 (12.3 per cent) died in the CCU and a further 58 died during their after-care, giving a total hospital mortality of 143 out of 693 (20.6 per cent). The CCU and hospital mortality in the 433 patients aged below 70 years were 9 and 14 per cent respectively

HYPOTENSION

Incidenc of hypotension

149 patients with AMI (22 per cent) had hypotension without signs of shock during their CCU stay 25 (4 per cent) were hypotensive already on admission and the remaining 124 patients (18 per cent) became hypotensive later on during the CCU stay The mean age of the 149 patient was 65 years which was the same as for the 489 patients without shock or hypotension. Nor did the delay between onset of symptoms and admission d ffer between these two groups, mean time being 8 hours in both groups. The mean CCU stay was 71 hours for the hypotension group and 50 hours for the rest.

Anamnestic data and clinical findings on admission

Table I shows the anamnestic data of the 149 patients with hypotension as compared with the 489 patients without shock or hypotension. A past history of hypertension was less common in patients with hypotension. Fainting or unconsciousness prior to admission was more common in this group No other significant differences were found between the groups.

Table shows the physical and ECG findings on admission. 46 per cent of the 149 patients with hypotension in CCU had ECG signs of an AMI which is significantly more than the 32 per cent in patients without shock or hypotension. Inferior infarcts predominated. Complete heart block, ventricular ectopic beats and ventricular tachycardia were also significantly more common

Table 1 Anamnestic data in the 149 patients with AMI and hypotension but not shock in CCU compared with the 489 patients without shock or hypotension.

	Patients with hypotension n=149	Patients without shock or hypotension n=489	P
	per cent	per cent	
Past history			
No previous angina pectoris	39	34	N.S.
Angina 1 week to 1 month prior to admission	11	18	N.S.
Angina more than 1 month prior to admission	50	48	N.S.
Previous myocardial infarction	28	34	N.S.
Heart failure	32	36	N.S.
Hypertension	22	37	<0.05
Valvular disease	7	3	N.S.
Diabetes	7	1	N.S.
Symptoms prior to admission			
No central chest pain	11	7	N.S.
Central chest pain without radiation	18	17	N.S.
Central chest pain with radiation	70	74	N.S.
Dyspnoea	43	42	N.S.
Fainting or unconsciousness	25	15	<0.01
Arrhythmic sensation	26	27	N.S.
Vomiting or sweating	79	71	N.S.
Physical or psychical effort before onset of symptoms	20	1	N.S.

Table 2 Physical and ECG findings on admission in the 149 patients with AMI and hypotension but not shock in CCU compared with the 489 patients without shock or hypotension

	Patients with hypotension n=149	Patients without shock or hypotension n=489	P
	per cent	per cent	
Unconsciousness	3	1	N.S.
Frank pulmonary oedema	9	6	N.S.
Left heart failure, frank pulmonary oedema excluded	31	34	N.S.
ECG signs of AMI	46	37	<0.01
Anterior AMI	17	13	N.S.
Lateral AMI	0	1	N.S.
Inferior AMI	17	9	<0.01
Anterolateral AMI	5		N.S.
Anteroinferior AMI	0	0	N.S.
Inferolateral AMI	5	6	N.S.
Anteroinferolateral AMI	1	0	N.S.
Supraventricular tachycardia	23	17	N.S.
Supraventricular bradycardia	5	4	N.S.
Atrial flutter	1		N.S.
Atrial fibrillation	13	8	N.S.
A V block I	6	3	N.S.
A V block II	3	1	N.S.
Complete heart block	5	1	<0.01
LBBB including hemiblocks	13	11	N.S.
RBBB	4	[illegible]	N.S.
Ventricular ectopic beats	30	15	<0.001
Ventricular tachycardia	8	1	<0.001
Ventricular fibrillation	1	1	N.S.
Ventricular standstill	1	0	N.S.

in the hypotensive group. The 149 patients were split into two groups, one including the 25 patients with hypotension already on admission and the other with the 124 patients who developed it later on (Table 3). A higher incidence of atrial fibrillation, A V block II, complete heart block, left bundle branch block and ventricular tachycardia was found in those with hypotension on admission, whereas only ventricular ectopic beats and ventricular tachycardia was significantly more common in those who developed hypotension. Those patients also had a positive ECG on admission significantly more often.

Mortality

The CCU mortality was 16 per cent for patients with hypotension and 3 per cent for patients without shock or hypotension. The figures for the after-care mortality were 15 and 6 per cent respectively giving a total hospital mortality of 31 and 9 per cent respectively.

SHOCK

Incidence of shock

55 patients with AMI (8 per cent) had shock during their CCU stay. 22 (3 per cent) were in shock already on admission and 33 patients (5 per cent) developed shock later on during their CCU stay. Thus, 60 per cent of the shock patients developed shock after admission. The mean age of the 55 patients with shock was 69 years and for the 638 patients without shock 66 years. The difference is not statistically significant. The mean time for the delay between onset of symptoms and admission was 7 hours for the shock patients and 9 hours for those without shock. The difference is not statistically significant. The mean CCU stay was 33 hours for the shock group and 55 hours for the rest.

Table 3 Physical and ECG findings on admission in the 25 patients with hypotension on admission and the 124 who developed hypotension in the CCU compared with the 489 patients without shock or hypotension

	Patients with hypotension on admission n = 25 per cent	P	Patients without shock or hypotension n = 489 per cent	P	Patients who developed hypotension n = 124 per cent
Unconsciousness	4	N.S.	1	N.S.	2
Frank pulmonary oedema	12	N.S.	6	N.S.	8
Left heart failure, frank pulmonary oedema excluded	40	N.S.	34	N.S.	79
ECG signs of AMI	36	N.S.	37	<0.001	48
Anterior AMI	8	N.S.	13	N.S.	19
Lateral AMI	0	N.S.	1	N.S.	0
Inferior AMI	16	N.S.	9	<0.05	17
Anterolateral AMI	4	N.S.	2	N.S.	6
Anteroinferior AMI	0	N.S.	0	N.S.	0
Inferolateral AMI	8	N.S.	6	N.S.	5
Anteroinferolateral AMI	0	N.S.	0	N.S.	
Supraventricular tachycardia	32	N.S.	17	N.S.	22
Supraventricular bradycardia	12	N.S.	4	N.S.	4
Atrial flutter	0	N.S.	2	N.S.	
Atrial fibrillation	28	<0.01	8	N.S.	10
A V block I	12	N.S.	3	N.S.	5
A V block II	16	<0.001	1	N.S.	1
Complete heart block	1	<0.001	1	N.S.	3
LBBB including hemiblocks	28	<0.05	11	N.S.	10
RBBB	8	N.S.		N.S.	3
Ventricular ectopic beats	24	N.S.	15	<0.001	31
Ventricular tachycardia	16	<0.001	1	<0.01	6
Ventricular fibrillation	4	N.S.	1	N.S.	1
Ventricular standstill	4	N.S.	0	N.S.	1

Anamnestic data and clinical findings on admission

Table 4 gives the anamnestic data of the 55 patients with shock and the 638 patients without shock. A history of fainting or unconsciousness prior to admission was more common in the shock group. No other significant differences were found between the two groups.

Table 5 shows the physical and ECG findings on admission. Left heart failure, ECG signs of AMI especially located anteriorly A V block I and II and ventricular tachycardia were significantly more common among the shock patients.

Splitting up the shock group as to whether shock was present on admission or developed later unconsciousness A V block I and II, ventricular tachycardia and ventricular standstill were more common in the 22 patients with shock on admission (*Table 6*), whereas ECG signs of AMI supraventricular tachycardia and right bundle branch block on admission were more common in the 33 patients who developed shock during the CCU stay

The prevalence of frank pulmonary oedema on admission was 9 per cent in the patients with shock on admission, 6 per cent in the shock developing patients and 7 per cent in the patients without shock. *None of the differences is statistically significant.* The prevalence of less severe left heart failure on admission was 41 per cent in the patients with shock on admission, 48 per cent in the shock developing patients and 33 per cent in the patients without shock. None of the differences is statistically significant.

The prevalence of shock on admission was 4 per cent in patients with frank pulmonary oedema on admission and 3 per cent in patients without fulminating pulmonary oedema. In patients with less severe left heart failure on admission the prevalence of shock was 4 per cent and in the remaining patients without signs of left heart failure 3 per cent.

Table 4 Anamnestic data in the 55 patients with AMI and shock compared with the 638 patients without shock.

	Patients with shock n=55 per cent	Patients without shock n=638 per cent	P
Past history			
No previous angina pectoris	24	30	N.S.
Angina 1 week to 1 month prior to admission	13	16	N.S.
Angina more than 1 month prior to admission	38	49	N.S.
Previous myocardial infarction	44	33	N.S.
Heart failure	38	36	N.S.
Hypertension	27	30	N.S.
Valvular disease	5	4	N.S.
Diabetes	4	11	N.S.
Symptoms prior to admission			
No central chest pain	15	8	N.S.
Central chest pain without radiation	9	17	N.S.
Central chest pain with radiation	76	69	N.S.
Dyspnea	47	42	N.S.
Fainting or unconsciousness	29	17	<0.05
Arrhythmic sensation	29	27	N.S.
Vomiting or sweating	80	73	N.S.
Physical or psychical effort before onset of symptoms	16	21	N.S.

Table 5 Physical and ECG findings on admission in the 55 patients with AMI and shock during the CCU period compared with the 638 patients without shock.

	Patients with shock n=55 per cent	Patients without shock n=638 per cent	P
Unconsciousness	5	2	N.S.
Frank pulmonary oedema	7	7	N.S.
Left heart failure, frank pulmonary oedema excluded	49	33	<0.05
ECG signs of AMI	60	37	<0.01
Anterior AMI	29	14	<0.01
Lateral AMI	0	1	N.S.
Inferior AMI	20	12	N.S.
Anterolateral AMI	4	3	N.S.
Anteroinferior AMI	0	0	N.S.
Inferolateral AMI	5	6	N.S.
Anteroinfero lateral AMI	2	0	N.S.
Supraventricular tachycardia	29	19	N.S.
Supraventricular bradycardia	7	5	N.S.
Atrial flutter	2	2	N.S.
Atrial fibrillation	15	10	N.S.
A V block I	11	4	<0.05
A V block II	9	1	<0.001
Complete heart block	4	[illegible]	N.S.
LBBB including hemiblocks	16	12	N.S.
RBBB	7	3	N.S.
Ventricular ectopic beats	25	19	N.S.
Ventricular tachycardia	11	3	<0.01
Ventricular fibrillation		1	N.S.
Ventricular standstill	4	0	N.S.

Incidence of left heart failure during the first 24 hours

There were 47 patients (85 per cent of the shock patients) who had shock within the first 24 hour period. The incidence of frank pulmonary oedema in these patients during the same period was 30 per cent, which is significantly more than 8 per cent in those without shock during the same period ($P < 0.001$). However 53 per cent of the patients with co-existing shock and frank pulmonary oedema during the first 24 hours, developed their fulminating pulmonary oedema within one hour prior to death.

Of the same 47 shock patients 64 per cent developed less severe degrees of left heart failure during the first 24 hours compared with 56 per cent for patients without shock. The difference is not statistically significant ($P > 0.05$).

In patients with frank pulmonary oedema during the first 24 hours, the incidence of shock during the same period was 20 per cent compared with a 5 per cent incidence of shock in those without frank pulmonary oedema ($P < 0.001$). In patients with less severe left heart failure during the first 24 hours, 7 per cent had shock during the same period while the shock incidence in patients without any degree of left heart failure was 2 per cent ($P < 0.01$).

Incidence of arrhythmias during the first 24 hours

Supraventricular tachycardia and bradycardia, A V block I and II, complete heart block, bundle branch block, ventricular tachycardia, ventricular fibrillation and ventricular standstill were significantly more common during the first 24 hours in patients with shock than in those without shock (Table 7).

Mortality

The CCU mortality was 84 per cent for patients with shock and 6 per cent for patients without shock. The corresponding after-care death rates

Table 6 Physical and ECG findings on admission in the 22 patients with shock on admission and the 33 patients who during the CCU stay developed shock, compared with the 638 patients without shock.

	Patients in shock on admission n=22 per cent	P	Patients without shock n=638 per cent	P	Patients who developed shock n=33 per cent
Unconsciousness	14	<0.01	2	N.S.	0
Frank pulmonary oedema	9	N.S.	7	N.S.	6
Left heart failure, frank pulmonary oedema excluded	41	N.S.	33	N.S.	48
ECG signs of AMI	45	N.S.	37	<0.001	70
Anterior AMI	9	N.S.	14	<0.001	42
Lateral AMI	0	N.S.	1	N.S.	0
Inferior AMI	23	N.S.	1	N.S.	18
Anterolateral AMI	0	N.S.	3	N.S.	6
Anteroinferior AMI	0	N.S.	0	N.S.	0
Inferolateral AMI	9	N.S.	6	N.S.	3
Anteroinferolateral AMI	5	N.S.	0	N.S.	0
Supraventricular tachycardia	36	N.S.	19	<0.05	36
Supraventricular bradycardia	14	N.S.	5	N.S.	3
Atrial flutter	0	N.S.	2	N.S.	3
Atrial fibrillation	14	N.S.	10	N.S.	18
A-V block I	18	<0.01	4	N.S.	6
A-V block II	18	<0.001	1	N.S.	6
Complete heart block	5	N.S.		N.S.	3
LBBB including hemiblocks	18	N.S.	12	N.S.	15
RBBB	0	N.S.	3	<0.05	12
Ventricular ectopic beats	32	N.S.	19	N.S.	33
Ventricular tachycardia	14	<0.05	3	N.S.	9
Ventricular fibrillation	5	N.S.	1	N.S.	0
Ventricular standstill	9	<0.001	0	N.S.	0

were 13 and 8 per cent, giving a total hospital mortality of 96 and 14 per cent, respectively.

Survival time

Of the patients with shock on admission 29 per cent had died within 3 hours, 38 per cent within 6 hours, 43 per cent within 12 hours and 52 per cent within 24 hours after admission. The mean CCU survival time in shock was 35 hours, range 1 to 111 hours. Of the patients developing shock 36 per cent had died within 3 hours after onset of shock, 61 per cent withing 6 hours, 76 per cent within 12 hours and 94 per cent within 24 hours.

Autopsy findings

The autopsy rate was 98 per cent. 12 per cent of the autopsied shock patients had ventricular septal defect or total or partial papillary muscle rupture. In a previous study on part of the present material, a significantly longer survival time after onset of shock was found in the presence of right ventricular hypertrophy at autopsy (Lunde et al. 1971).

Table 7 Arrhythmias during the first 24 hours in patients with and without shock during this period

	Patients with shock n=47 per cent	Patients without shock n=644 per cent	P
Supraventricular tachycardia	70	41	<0.001
Supraventricular bradycardia	47	19	<0.001
Atrial flutter	4	4	N.S.
Atrial fibrillation	23	14	N.S.
A-V block I	3	9	<0.001
A-V block II	30	6	<0.001
Complete heart block	26	4	<0.001
LBBB, including hemiblocks	36	14	<0.001
RBBB	15	4	<0.001
Ventricular ectopic beats	38	25	N.S.
Ventricular tachycardia	62	35	<0.001
Ventricular fibrillation	26	4	<0.001
Ventricular standstill	45	5	<0.001

COMMENTS

DEFINITION

The criteria for the diagnosis of cardiogenic shock have been much disputed. The problem was reviewed by Binder et al. (1955) and more recently by Sloman and Hunt (1971). According to WHO (1970) "shock in acute myocardial infarction is characterized by a marked fall of arterial blood pressure (systolic usually below 85 mm Hg) cold, clammy sweating skin, cyanosis, weak steady pulse, oliguria, mental confusion and sometimes coma." However hypotension may be present in the absence of shock and has been reported to occur in 8 to 16 per cent of patients with AMI (Lown et al. 1967a and 1967b and Sloman and Hunt 1971). In one series (Lown et al. 1967b) hypotension carried a mortality of 21 per cent and in the series of Sloman and Hunt (1971) the mortality was 20 per cent.

On the other hand all shock symptoms may be present without hypotension especially in previously hypertensive patients. In a known hypertensive patient a fall of over 30 mm Hg below previously known basal level is considered to constitute hypotension (Wan et al. 1971 and Sloman and Hunt 1971). The last criteria, i.e. a systolic blood pressure 30 mm Hg below prior basal level for 30 minutes or longer was also used by Swan et al. (1970). Besides, they and others have used the criterium of intraarterially measured systolic pressure below 90 mm Hg.

INCIDENCE OF SHOCK

The incidence of shock due to AMI varies between 7 and 23 per cent in the literature (Braunwald 1967 Killip and Kimball 1967 Lawrie et al. 1967 Lown et al. 1967b Wallace et al. 1967 Pentecost and Mayne 1968 Pantridge 1970, Scheidt et al. 1970, Swan et al. 1970 Thompson et al. 1971 and Wan et al. 1971). The lowest incidence (7 per cent) was reported by Pantridge (1970) with a mobile coronary care unit For patients below 70 years and seen within an hour after onset of symptoms the incidence has recently been reported to be as low as 3.5 per cent (Adgey et al. 1971) In the present study of 693 patients with AMI the incidence of shock was 8 per cent. Especially because of different criteria in different series, comparisons are not meaningful. Binder et al. (1955) in a literature review reported on the inverse relationship between incidence of shock and mortality rates in shock, i.e. the lower the incidence, the higher the mortality

MORTALITY

The mortality from shock is reported to vary between 59 to 100 per cent (Day 1965 Braunwald 1967 Killip and Kimball 1967 Kuhn 1967 Lawrie et al. 1967 Lown et al. 1967b, Wallace et al. 1967 Scheidt et al. 1970, Swan et al. 1970 and Wan et al. 1971). The hospital mortality for shock in the present series was 96 per cent. It has been shown by Pantridge (1970) that the use of mobile CCU also reduces the total hospital mortality in shock.

AGE

Scheidt et al. (1970) and Wan et al. (1971) found the shock patients to be older than the non-shock patients. In the present study there was no significant difference between the two groups.

INTERVAL FROM ONSET OF INFARCTION SYMPTOMS TO ONSET OF SHOCK

A majority of shock patients of the present series was not in shock on admission. 6 per cent developed shock within 3 hours after onset of major symptoms, 4 per cent within 6 hours, 33 per cent within 12 hours and 64 per cent within 24 hours. Similar figures were also found by Scheidt et al. (1970). They found that shock developed within 24 hours of onset of symptoms in only half the group.

ANAMNESTIC DATA, PHYSICAL AND ECG FINDINGS

Like Scheidt et al. (1970) no difference in delay from onset of symptoms to admission incidence of previous myocardial infarction angina pectoris, systemic hypertension or diabetes was found in the present series. A history of previous left heart failure was not more common in patients with shock in the present series in contrast t the report by Wan et al. (1971).

No difference in the site of myocardial infarction was observed by Scheidt et al. (1970) between shock and non-shock patients. In the present study however anterior infarcts were more common in the shock patients than in patients without shock ($P < 0.01$). In contrast, patients with hypotension without shock were found to have inferior AMI more often.

Regarding frank pulmonary oedema and shock as the most severe manifestations of left ventricular damage, it is interesting that they are not co-existing in a significant degree on admission but during the first 24 hours they are. However more than half of these patients developed their fulminating pulmonary oedema in the terminal phase of shock within one hour prior to death. Most of the shock patients do not have frank pulmonary oedema and vice versa.

Stock et al. (1967) found a significantly higher incidence of major arrhythmias (atrial fibrillation, supraventricular tachycardia, nodal tachycardia, A V block I and II, complete heart block, bundle branch block, ventricular tachycardia or ventricular fibrillation) in patients with shock due to AMI than in patients without shock. Wan et al. (1971) recently reported that cardiogenic shock very often was complicated by arrhythmias. 76 per cent of patients with shock developed complete heart block, ventricular fibrillation, atrial fibrillation or bundle branch block. On the other hand, serious cardiac arrhythmia rarely preceeded the onset of shock in the series of Scheidt et al. (1970). In the present study a higher incidence of A V block I and II and ventricular tachycardia was found on admission in patients with shock. However as can be seen in Table 6 this higher incidence is confined only to those patients in shock on admission, whereas patients not in shock on admission but later developing it, did not differ significantly from patients without shock.

SURVIVAL TIME

In the present series 52 per cent of the patients with shock on admission had died by the end of the first 4 hour period. Wan et al. (1971) found that 55 per cent had died by the end of day 1 after admission.

In a previous study on part of the present material a significantly longer survival time after onset of shock was found in the presence of right ventricular hypertrophy at autopsy (Lunde et al. 1971). However it could not be concluded whether the hypertrophy existed prior to infarction or developed following it. The common causes of right ventricular hypertrophy i.e. left heart failure and pulmonary disease were not found to be over represented in the hypertrophy group. The development of right ventricular hypertrophy seems to be rapid in experimental pulmonary artery constriction as shown in cats by Spann et al. (1967) where the right ventricular weight was nearly doubled in 2 days. The pressure load on the right ventricle in AMI would reasonably seem to be much less than in these experiments, but the load necessary for producing right ventricular hypertrophy is not known.

AUTOPSY FINDINGS

Rupture of a myocardial infarct with cardiac tamponade ventricular septal defect or papillary muscle rupture were considered as a cause of cardiogenic shock in AMI in a review by Agress and Binder 1957. However the clinical course of cardiac tamponade in AMI due to rupture of the free ventricular wall does not usually last long enough to allow for a diagnosis of shock (Björck et al. 1972 and Mogensen et al. 197?).

In the present series of autopsied shock patients no one had rupture of the free ventricular wall with tamponade. Ventricular septal defect and total or partial papillary muscle rupture were not found altogether in more than 12 per cent of the autopsied shock patients.

SUMMARY

Shock and hypotension have been studied in 69? consecutive patients with acute myocardial infarction treated in a CCU. The CCU mortality

was 12.3 per cent and the total hospital mortality 20.6 per cent.

Incidence of shock was 8 per cent. 40 per cent of the shock patients had the complication already on admission and the rest developed it during their CCU stay ECG signs of acute myocardial infarction, especially located anteriorly supraventricular tachycardia and right bundle branch block on admission were significantly more common in patients who developed shock during the CCU stay than in those without shock. Major arrhythmias were significantly more common during the first 24 hours in all patients with shock during the same period compared with those without shock. The CCU and hospital mortality of shock was 84 and 96 per cent respectively

The incidence of hypotension without shock symptoms was 22 per cent, and the CCU and hospital mortality was 16 and 31 per cent respectively

PART II
Central hemodynamics

The aim of this part of the study was to measure the central hemodynamics in patients with shock complicating AMI and to relate some measured parameters to clinical findings.

MATERIAL

All patients included in the present study had ECG changes compatible with AMI and clinical signs of shock according to the criteria previously presented (page 10). Thus, they had a palpatory systolic blood pressure below 90 mm Hg and at least 4 of the following 5 symptoms: mental confusion or unconsciousness, cold skin, urine output less than 20 ml per hour peripheral or general cyanosis and metabolic acidosis.

During the period of study December 1 1970 to December 1 1971 17 patients fulfilled these shock criteria. Five patients were admitted when the team was unavailable and therefore not included in the hemodynamic study. Three patients were in severe shock on admission and died within 3 hours before any hemodynamic data had been obtained. This leaves 9 patients who were investigated when in shock. Seven of the 9 patients were directly admitted to the CCU at Serafimerlasarettet and 2 patient were referred from other hospital in Stockholm because of shock complicating AMI

METHODS

The general methods used in the CCU including admission criteria, routine investigations, diagnostic criteria, therapeutic policy and discharge criteria have been presented previously (page 8 to page 11). The hemodynamic measurements were performed as soon as possible following admission (for patients in shock already on admission) or following the development of shock. The presented data will be the pressure values obtained simultaneously with the first cardiac output determinations and these results will be related to the clinical findings from the same time.

The patients were investigated in their beds in the CCU in supine position and usually breathing oxygen. No patient had received any drug within 4 hours prior to the measurements.

PRESSURE MEASUREMENTS

Catheters were placed in the ascending aorta, the superior vena cava and the main pulmonary artery without help of fluoroscopy

The aortic catheter was a 75 cm long teflon catheter internal diameter 0.75 mm, external diameter 1.10 mm (Stille Werner Stockholm, Sweden). It was generally introduced by the percutaneous Seldinger technique (1953) into the brachial artery. The catheter was connected to a multiple section tap (Ole Dich, Hvidovre Denmark), and a pressure transducer (EMT 34 Elema Schonander Solna, Sweden). The whole system had resonance peak at frequency 1 18 Hz.

In some patients the *central venous catheter* was introduced via an antecubital vein, usually after a cut down. A 55 cm long teflon catheter was used with inner diameter 1.65 mm and outer diameter 2.15 mm (Stille Werner Stockholm, Sweden). The catheter with connections was found to have resonance peak at a frequency of 25 Hz. In the remaining patients the right internal jugular vein was used percutaneously (Brantiwaite and Bradley 1968) for the introduction of 20 cm long nylon catheter internal diameter 0.73 mm, exter

nal diameter 0.92 mm (Portex, Kent, England). This system was found to have a resonance peak at a frequency of 22 Hz.

The pulmonary artery catheter was in some patients a 150 cm long soft flow guided polyethylene catheter internal diameter 0.76 mm, external diameter 1.22 mm (Stille-Werner Stockholm, Sweden), which was introduced through the antecubital venous catheter The outer end of the catheter was put onto a needle hilt. The system was found to have a resonance peak at a frequency of 28 Hz. In other cases a 108 cm long nylon catheter inner diameter 0.75 mm, outer diameter 0.92 mm (Devices, London, England) was inserted into the right internal jugular vein and advanced to the pulmonary artery This catheter has a thermistor mounted in its end and some cm away there is a side hole. This system was found to have a resonance peak at a frequency of 14 Hz.

When passing the pulmonary artery catheter through the right ventricle a few ventricular ectopic beats or a short run of ventricular tachycardia was commonly provoked. No other complications occurred.

The position of the catheters were in some instances controlled by chest X-ray after filling the catheters with a contrast medium. The catheters were flushed intermittently with heparinized isotonic saline.

Aortic, central venous and pulmonary artery pressures were usually measured every hour Hydrostatic standards were used and pressures are given with a reference point 5 cm below the level of the fourth sterno-costal joint. Recordings were obtained by a multi-channel ink jet recorder (Elma Schönander Solna, Sweden). Mean pressures were obtained by electrical integration. The aortic pressures are given as means of 5 cycles and the pulmonary artery and central venous pressures as means of 10 cycles.

Great care was devoted to sterility and fixation of the catheters as these were used continuously for up to 6 days. No prophylactic antibiotic therapy was used. No local infection around the catheters or any other complication was observed.

Comments

Pulmonary artery catherization was performed in order to obtain the best possible indirect measure of left ventricular filling pressures. The pulmonary artery diastolic pressure has been shown to correlate well with the left atrial mean pressure in the absence of pulmonary disease (Kaltman et al. 1966 Bouchard et al. 1969 and Forsberg 1971). Jonsson and Sanal (1969) in an investigation of 64 patients with leftsided valvular disease, but without pulmonary disease, found a good relationship between pulmonary artery diastolic pressures and left atrial mean pressures for pulmonary artery diastolic pressures up to 30 mm Hg. Lassers and colleagues (1970) found in patients with AMI that pulmonary artery diastolic pressures closely reflected the mean pulmonary arterial wedge pressure in the absence of obstructive airways disease.

The technique of flow guided catheterization of the pulmonary artery was developed by Dotter and Straube (1962) and has since then been used by several authors (Bradley 1964 Fife and Lee 1965 Vogel et al. 1965 Bevegård et al. 1966, Valentine et al. 1966 Fluck et al. 1967 Pain et al. 1967 Balcon et al. 1968 Stannard et al. 1968 and Sjögren 1970). Two instances of ventricular fibrillation have been reported in association with the procedure, both in patients with AMI (Schuren et al. 1970 and Sjögren 1970). Beside these, no serious complications have been reported.

The inaccuracy in auscultatory and palpatory methods of blood pressure measurements in shock has been shown by Cohn (1967) Direct arterial pressures were considerably higher than the cuff pressures obtained by auscultation or palpation of the brachial artery in 18 patients with shock and with high peripheral vascular resistance. This discrepancy was not observed in 21 hypotensive patients with low or normal resistance. Failure to recognize that low cuff pressures do not necessarily indicate arterial hypotension may lead to errors in therapy

CARDIAC OUTPUT DETERMINATIONS

The cardiac output was determined at irregular intervals but at least 4 times a day The dye dilu-

tion method was used in all patients (Hamilton et al. 1928a, Hamilton et al. 1928b Moore et al. 1929 Kinsman et al. 1929 and Hamilton et al. 1931) and in three patients the thermal dilution method was also applied (Branthwaite and Bradley 1968)

For the dye dilution method indocyanine green (Cardiogreen, Hynson Westcott and Dunning, England) 5 or 10 mg was injected into the pulmonary artery or sometimes into the superior vena cava. The injection was made manually as rapidly as possible with a syringe according to Grimby and Nilsson (1963) This method allows for one ml of the dye solution to be flushed rapidly by 9 ml of saline at injection. Calibration was performed for each patient using at least four different dye concentrations.

Arterial blood was withdrawn by a specially constructed pump at a constant rate of 20 ml per min. and was reinfused into the patient after each estimation. The withdrawn blood was analyzed for dye with a Beckman cardiodensitometer (Spinco Division of Beckman Instruments, Inc Palo Alto California, USA) which involves automatic counting of the curve area according to Hepner et al. (1964). This method of calculating the area under the curve was tested on a random sample of 22 curves and the results were compared with those obtained by the conventional method of summing the area beneath the ascending limb and the area obtained by the semilog replot of the decending limb (Kinsman et al. 1929). There was good agreement (r = 0.95 P < 0.001) between the two methods. No statistical significant difference was found between the means of the curve areas calculated according to one or the other method.

All cardiac output curves were also manually calculated according to Dow (1955).

In 3 of the 9 patients the cardiac output was also estimated with thermal dilution The method used is that described by Branthwaite and Bradley (1968) A solution of 10 ml 5.5 per cent glucose at room temperature was injected as a thermal indicator into the superior vena cava and detected in the pulmonary artery by a thermistor The thermistor catheter (page 70) is attached via a cable to the calibration socket in the cardiac output computer (Cardiac output computer type 3750 Devices Instruments Limited, Herts, England). Each thermistor catheter has its own calibration socket and the thermistor is calibrated on manufacturing.

The glucose solution for injection was stored in capped 10 ml plastic syringes placed in a glass box, which was kept in a wide necked vacuum flask. Sterile saline solution was poured into and outside the glass box and all was left for one hour for temperature equilibration. An injectate thermistor was placed into the saline solution outside the glass box, and connected with the cardiac output computer

At every determination flushing of the catheters was interrupted to minimize the influence on the thermistor The saline injection was made by hand as fast as possible. The computed cardiac output was used. In the present study maximally 10 cardiac outputs in 14 min. were performed.

The stroke volume was obtained by dividing the cardiac output by the heart rate from the simultaneous electrocardiogram. The cardiac index was calculated by dividing the cardiac output by the total body surface area (BSA) obtained from a nomogram based on the formula of DuBois (1916).

Comparison of methods for cardiac output determination

Good correlation has been found between cardiac outputs determined by the dye dilution technique and by Fick's method in man (Hamilton et al. 1948, Werko et al. 1949 Johnson 1951 Kopelman and Lee 1951 Doyle et al. 1953 Smith et al. 1954 Eliasch et al. 1955 Rickardson et al. 1959 Forsberg 1964 and Sjogren 1970).

It has been shown that in low output states, the recirculation of dye may cause a slow downslope of the dye dilution curve so that the area beneath the curve will be overestimated and the cardiac output underestimated (Dow 1955 MacKenzie 1964 and Oriol and McGregor 1967). Dow (1955) empirically found a constant relation between the area under the ascending part of the dye dilution curve and the total area. The formula constructed

took into consideration appearance time, peak concentration time and peak concentration. He suggested that this formula should be used for curves where the time for the descending part of the curve to reach one tenth of peak concentration is more than 3.0 to 3.5 times the appearance time.

Oriol and MacGregor (1967) found a good agreement in 7 determinations of cardiac output in 4 patients in shock between dye curve estimates based on Dow's formula and direct Fick estimates, whereas curves measured by conventional Hamilton technique gave lower cardiac output values.

Dow made the dye injections in an antecubital vein and sampled from the femoral artery whereas Oriol and MacGregor injected in the low superior vena cava or right atrium and withdrew blood from the brachial artery. Approximating the injection and sampling sites will reduce the time for recirculation.

Since the principle of estimating cardiac output by thermal dilution was introduced by Fegler (1953) in animal experiments, several techniques have been developed with different injection and detecting sites. Many reports exist on comparisons of cardiac output determination by thermal dilution and dye dilution (Fegler 1953 and 1954, Goodyear et al. 1959, Froněk and Ganz 1960, Solomon 1969, Olsson et al. 1970 and Ganz et al. 1971) as well as with Fick's method (Fegler 1953 and 1954, Goodyear 1959, Froněk and Ganz 1960 and Branthwaite and Bradley 1968). Both good correlation and reproducibility has been shown. Solomon (1969) also showed this experimentally in low cardiac output states. Ganz et al. (1971) concluded: "there is virtually no recirculation, so that a simple integrator can be used for determination of the area beneath the thermodilution curve"

)

$$\text{Area} = \frac{PC \times PCT}{(k_1 - k_2) \times \frac{PCT}{AT}}$$

PC = peak concentration
PCT = peak concentration time
AT = appearance time
k_1 = .98 and k_2 = 0.91 (Constants established by Dow 1955 and slightly modified by Sekelj et al 1966).

In the present study the problem of best estimating cardiac output in shock was met with in three ways. Firstly, the dye dilution curve areas were calculated with the conventional method according to Hepner as well as with Dow's correction formula. Secondly, the sites of dye injection and sampling were approximated by injection into the pulmonary artery and sampling in the central aorta. In two patients, cardiac output determinations obtained by superior vena cava injections could be compared with those obtained by pulmonary artery injections made within a very short time and with the same sampling site. Thirdly, thermal as well as dye dilution was performed in three patients. Comparisons were made between thermal dilution cardiac outputs on one hand and cardiac outputs estimated according to Hepner's and Dow's methods on the other.

The cardiac output curves obtained by the dye dilution method and calculated according to Dow (1955) and Hepner (1964) were compared for altogether 134 determinations in 8 patients. The cardiac output calculated according to Hepner's method varied between 1.0 to 5.8, mean 2.8 (S.D

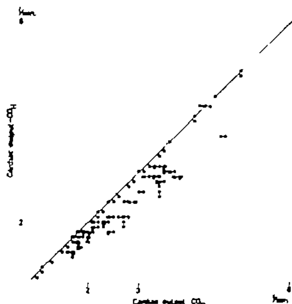


Fig. 1. Plot of cardiac output determinations calculated according to Hepner's method (CO) and Dow's method (CO_D) in 8 patients. Line indicates identity.

1.1) lit. per min. and according to Dow's method between 1.0 to 7.0 mean 3.. (S.D. 1.1) lit. per min. The difference is significant ($P < 0.01$). The results is presented in Fig. 1 and shows good correlation ($r = 0.94$, $P < 0.001$). The difference between the calculations according to Hepner and according to Dow was greatest for low cardiac outputs.

The reproducibility of the dye technique was tested by comparing 100 paired estimations performed within 5, mean 3.6 (S.D. 1.0) min. in 8 patients. The result is illustrated in Fig. 2 and 3. The methodological error was 0.31 lit. per min for the Hepner estimations and 0.33 lit. per min. for Dow's method, which is 11 and 10 per cent of the mean values respectively.

Comparison between different injection sites was made in two patients. The dye injection was made into the superior vena cava and into the pulmonary artery, each at 5 instances, 5 to 9, mean 6.4 min. apart, and detected at the same site in the central aorta. When calculated according to Hepner the mean of the cardiac output determinations obtained by the superior vena cava injections was 1.9 lit. per min. and obtained by the injections into the pulmonary artery ..1 lit. per min. The difference is not statistically significant ($P > 0.05$). The means of the same cardiac output determinations calculated according to Dow are ..4 and .... lit. per min. respectively. Nor is this difference statistically significant ($P > 0.05$).

Cardiac outputs obtained by thermal dilution were compared with cardiac outputs measured by dye dilution in 3 patients. The paired determinations were obtained within to 10, mean 5.0 (S.D. 3.0) min. The results are given in Table 8 and Fig. 4 and 5. Cardiac outputs obtained by dye dilution according to Hepner were 1.1 lit. per min. (28 per cent) lower than with thermal dilution ($P < 0.001$). On the other hand there was no significant difference when comparing the same dye dilution curves calculated according to Dow and the thermal dilution values (difference 0.2 lit. per min., 5 per cent, $P > 0.05$).

The reproducibility of the thermal dilution technique with the Devices cardiac output com

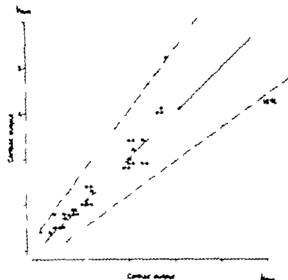


Fig. 2. Plot of repeated cardiac output estimations performed within 5 min. by the dye dilution method and calculated according to Hepner. One hundred paired estimations in 8 patients. Lines indicate identity ± 15 per cent.

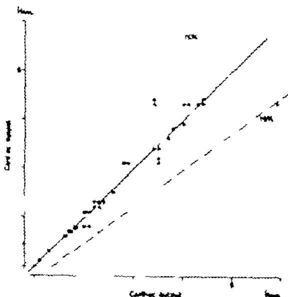


Fig. 3. Plot of repeated cardiac output estimations performed within 5 min. by the dye dilution method and calculated according to Dow. One hundred paired estimations in 8 patients. Lines indicate identity ± 15 per cent.

T bl 8 Comparison of cardiac output determined by thermal dilution and dye dilution in 3 patients at 12 instances. CO_{TD} = cardiac output by thermodilution. CO_H = cardiac output by dye dilution calculated according to Hepner CO_D = cardiac output by dye dilution calculated according to Dow

	Mean l/min.	Difference between means l/min.	P
CO_H	2.9		
		1 1	<0.001
CO_{TD}	4.0		
		0 2	>0.05
CO_D	3.8		

puter was tested by comparing 53 paired estimations in 3 patients performed within 5 min., mean 1 7 min. (S.D 1.0). The result is shown in Fig. 6. The methodological error was 0.56 lit. per min., which is 14 per cent of the mean value.

On the basis of these investigations it was considered reasonable to use the dye dilution curves calculated according to Dow for all cardiac ouput values in the present study

DERIVED HEMODYNAMIC PARAMETERS

Systemic vascular resistance was calculated according to the formula.

(mAo—CVP)/CO

where mAo = mean aortic pressure, CVP = central venous pressure and CO = cardiac output.

Left ventricular stroke work was expressed in grammeters and calculated according to the formula

$SV \times (Ao_{ms} - PA_d) / 0.0136$

where SV = stroke volume, Ao_{ms} = mean systolic pressure and PA_d = pulmonary artery diastolic pressure.

The product of aortic systolic pressure and heart rate was used as an index of myocardial oxygen demand (Gerola et al. 1957 Katz and Feinberg 1958 Katz 1963 Sullivan and Gorlin 1967 and Holmberg 1971)

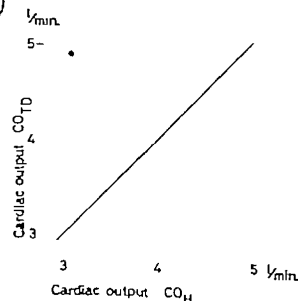


Fig 4 Plot of cardiac output measured by the dye dilution method according to Hepner (CO_H) and the thermal dilution method (CO_{TD}) in 3 patients (12 estimations). Line indicates identity

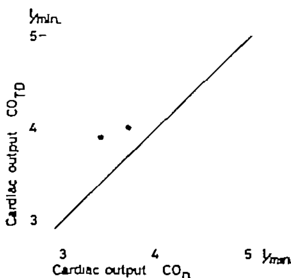


Fig 5 Plot of cardiac outputs measured by the dye dilution method according to Dow (CO_D) and the thermal dilution method (CO_{TD}) in 3 patients (12 estimations). Line indicates identity

Table 9 Clinical findings in the 9 patients evaluated hemodynamically

Case	Age	Sex	Body surface area	Time from onset of symptoms to admission	Time from admission to onset of shock	Time in shock	Previous myocardial infarction	History of hypertension	ECG site of infarction	Rales	Respiratory rate	Urine output	CCU survival	Akinetic, dyskinetic area
			m²	hrs	hrs	hrs	No				per min	ml/hr		per cent of left ventricle
AM	74	M	1.84		b)	1	1	—	inferolateral	+	44	0	+	35
EB	71	M	1.82	)		23	1	+	inferior	+	20	10	+*)	
SR	59	M	1.79	5	b)	37	0	—	inferolateral	—	24	0	—	100
AA	67	M	1.87	)	b)	8	1	—	anterior	—	26	5	—	100
EH	58	M	1.90	3		12	0	—	inferolateral	+	28	16	—	50
SA	67	M	1.65	a)	b)	8	0	—	anterior	—	3	10	+	60
EP	51	M	09	1	19	3	0	—	anterolateral	—	_4	1	+	55
MK	59	F	1.53	3	9	3	0	+	anterior	—	16	0	—	65
HJ	65	F	1.42	1	9	8	3	+	anterior	+	37	4	—	75

) = referred from other hospital
b) = in shock already on admission
) = at the time of hemodynamic evaluation
) = hospital survival

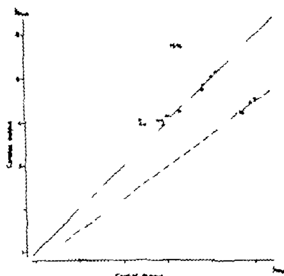


Fig. 6 Plot of paired cardiac output estimations by thermal dilution CO ... 52 paired estimations in 3 patients. Lines indicate identity ± 15 per cent

RESULTS

The pressure measurements obtained in association with the first cardiac output determinations are given in Table 10 together with the clinical findings at the same time, 1 to 22, mean 7 hours after onset of shock.

A. CLINICAL RESULTS

Of the 9 patients (Table 9) age 51 to 74 years, mean 63 years, 7 were men and 2 women. Delay from onset of symptoms to admission was 1 to 5 hours, mean 3 hours. Four patients were in shock on admission. The remaining 5 patients developed shock during their CCU stay _ to 19 mean 8 hours after admission and 5 to 20, mean 12 hours following onset of symptoms. The time in shock varied in the 9 patients from 3 to 37 hours, mean 14 hours.

Four of the 9 patients had a history of previous myocardial infarction and 3 of hypertension. Five had ECG signs of anterior or anterolateral AMI and the rest inferior or inferolateral.

Table 10 Hemodynamic findings in the 9 patients studied

Pt	Time from onset of shock to study	Rhythm a)	Heart rate	Palpatory blood pressure	Aortic blood pressure	Mean aortic blood pressure	Central venous pressure	Pulmonary artery pressure	Cardiac output	Stroke volume	Systemic vascular resistance	Left ventricular stroke work
	hrs		per min.	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min	ml	units	gm-m/beat
AM	9	SR	110	60	59/47	50	10	31/10	2.1	19	19	12
EB	5	PM	90	u	54/41	44	11		1.0	11	33	
SR	6	SR	98	u	57/4	48	3	37/22	1.8	18	25	7
AA	8	SR	114	u	76/54	6[illegible]	8	25/16	3.5	31	15	1
EH	8	SR	100	80	92/68	82	4	50/38	3.4	34	23	20
SA	1	AF	100	70	76/56	66	—	29/14	3.3	33	21	[illegible]5
EP	1	SR	110	85	110/80	96		33/20	[illegible]2	20	43	[illegible]3
MK	1	SR	123	75			10	41/30				
HJ	22	SR	110	80	100/61	75	9	1/11	4.5	41	15	42

a) PM = pace maker induced rhythm. SR = sinus rhythm. AF = atrial fibrillation
u = unobtainable blood pressure

Heart rhythm and rate

One patient had complete A V block and was paced at a rate of 90 per min. One patient had atrial fibrillation and the remaining patients had sinus rhythm. ECG showed right bundle branch block in one patient. The heart rates varied between 90 and 1_3 mean 106 beats per min.

Heart failure

Basal rales could be heard in 4 patients. No one had frank pulmonary oedema, but two patients developed it later on. Chest X-ray performed in 6 patients some time during their shock state, showed various degrees of pulmonary congestion in all but one.

Respiratory rate

The respiratory rate varied between 16 and 44, mean 27 per min

Urine output

Urine output varied between 0 and 16, mean 6 ml per hour. Three patients were anuric.

B. HEMODYNAMIC RESULTS

The hemodynamic findings are shown in Table 10

Arterial blood pressure

The aortic systolic blood pressure varied between 54 and 110 mean 78 mm Hg and the palpatory blood pressure obtained at the same time between 60 and 80 mean 75 mm Hg (Fig. 7). The palpatory blood pressure was unobtainable in 3 patients whereas the simultaneously obtained aortic systolic pressures were 54 57 and 76 mm Hg.

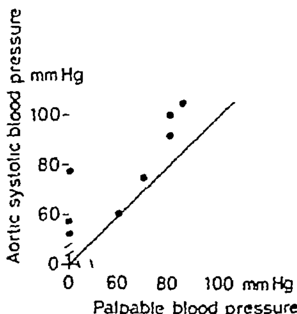


Fig. 7 Plot of palpable blood pressure and aortic systolic blood pressure in 8 patients with shock complicating AMI. Line indicates identity

The diastolic pressure could not be obtained by auscultation in any patient. The aortic diastolic pressure varied between 41 and 80 mean 56 mm Hg.

The aortic catheter was kept in the patients from 14 to 136 mean 61 hours. No complications were observed.

Central venous pressur

The central venous pressures ranged f om —.. to +11 mm Hg with a mean of +6 mm Hg. The central venous pressure was above 8 mm Hg in 4 patients, between 4 and 8 mm Hg in 2 patients and below 4 mm Hg in 3 patients. The 2 patients with the lowest central venous pressures (case SA, — mm Hg and case EP + mm Hg) responded favourably to rapid infusion of 5.5 per cent glucose, which was hemodynamically evaluated (page 30).

The central venous catheter was kept in the patients f om 3 to 135 mean 54 hours and no complications were observed.

Pulmonary artery pressur

The systolic pressures of the pulmonary artery ranged from 1 to 50 mean 33 mm Hg. The diastolic pressures varied between 10 and 38 mean 20 mm Hg. Six out of 8 patients, in whom pulmonary artery pressures were obtained, had a diastolic pressure above 11 mm Hg and 3 over 20 mm Hg. Two patients had a diastolic pressure of 30 mm Hg or more and none of these were in frank pulmonary oedema at that time.

As shown in Fig. 8 there was no correlation between central venous pressure and simultaneous diastolic pressure f the pulmonary artery (r = —0.095 P > 0.05)

There was no correlation between the diastolic pressur of the pulmonary artery and the respiratory rate (= —0.61 P > 0.05)

The pulmonary artery catheter was kept in the patients from 1 to 93 mean 41 hours. No complications were observed.

Cardiac output and stroke volume

The cardiac output ranged from 1.0 to 4.5 mean ..7 lit. per min. Four out of 8 patients, in whom cardiac outputs were obtained, had a cardiac output below ..5 lit. per min. The stroke volume ranged from 11 to 41 mean 26 ml.

Systemic ascular esistance and left v ntricular stroke work

The systemic vascular resistance ranged from 15 to 43 mean 24 units. Six patients had a systemic vascular resistance of 19 units or more.

Left ventricular stroke work varied between 7 and 4.., mean 19 grammeter per beat.

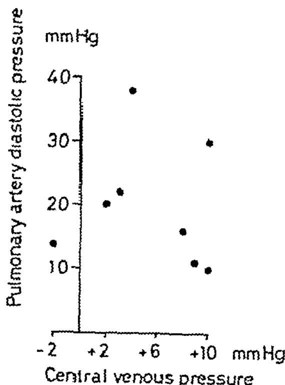


Fig. 8 Central venous pressur in elation to pulmonary artery diastolic pressure in 8 patients with shock complicating acute myocardial infarction (= —0.095 P > 0.05).

COMMENTS

Detailed hemodynamic studies in shock complicating AMI are to date limited to a rather small number of patients because of the difficulties inherent in investigating these patients. In general, low cardiac output, stroke volume and arterial pressure and elevated heart rate, systemic vascular resistance and central venous pressure are reported (Freis et al. 1952, Gilbert et al. 1954 Smith et al. 1954 Gammill et al. 1955 Gunton et al. 1957 Mac Kenzie et al. 1964 Thomas et al. 1965 Gunnar et al. 1967 Shillingford and Thomas 1967 Smith et al. 1967 Weil and Schubin 1968, Cohn et al. 1969 Fantini and Scarpelli 1969 Hamosh et al. 1969 Bradley et al. 1970, Scheidt et al. 1970 and Swan et al. 1970).

Correspondingly in the present study low cardiac output, stroke volume and aortic blood pressure and elevated systemic vascular resistance and central venous pressure were generally found. However as can be seen in Fig. 9 and 10 there was considerable variation between the patients. Four patients had cardiac outputs below 2.3 lit. per min. but their aortic systolic blood pressure varied between 54 and 110 mm Hg. This variation in hemodynamic pattern has previously been described by Smith et al. (1954) and more recently by Swan and colleagues (1970) and Scheidt et al. (1970). Three patients had a systolic aortic pressure above 90 mm Hg. Yet, all were in shock according to the given criteria, which include a palpatory systolic blood pressure below 90 mm Hg.

Gunnar et al. (1967) compared the hemodynamic findings in 11 patients with AMI not in shock and 20 patients with AMI and shock. The criteria for shock were the same as in the present study except for the arterial blood pressure, which had to be below 80 mm Hg or below 90 mm Hg for previously hypertensives. Cardiac output showed a group mean of 3.8 and 2.6 lit. per min., stroke volume 43 and 27 ml, mean aortic pressure 9? and 57 mm Hg and systemic vascular resistance 26 and 25 units respectively These values for the shock group corresponded well with the results in the present study where the cardiac output was ?.7 lit. per min., stroke volume 26 ml, mean aortic pressure 65 mm Hg and systemic vascular resistance 24 units.

Scheidt and colleagues (1970) performed hemodynamic studies in 19 patients with shock in association with AMI. Their shock criteria were similar to those in the present study Cardiac index and stroke index were reduced in all patients. Cardiac index varied from 0.4 to 2.1 mean 1.1 lit. per min. per m² BSA (body surface area) and stroke volume index respectively 4 to ?3 mean 10 ml per beat per m² BSA. Total peripheral resistance was generally increased (range 900 to 5000 dynes sec cm⁻⁵) In the present study cardiac index varied between 0.5 and 3.2, mean 1.6 lit. per min. per m² BSA and stroke volume index between 6 to 29 mean 15 ml per beat per m² BSA.

Swan et al. (1970) compared the hemodynamic data of 15 non-shock and 16 shock patients with



Fig 9 Hemodynamic findings in 9 patients with shock complicating AMI HR = heart rate RR = respiratory rate A = aortic systolic pressure mAo = mean aortic pressure Mean and S.D indicated by E.
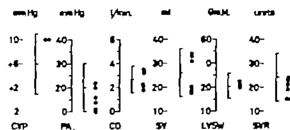


Fig 10 Hemodynamic findings in 9 patients with shock complicating AMI CVP = central venous pressure PA$_d$ = pulmonary artery diastolic pressure CO = cardiac output SV = stroke volume LVSW = left ventricular stroke work SVR = systemic vascular resistance Mean and S.D indicated by E.

AMI. Shock was defined as a systolic arterial pressure, directly measured below 90 mm Hg or 30 mm Hg below prior basal level for 30 minutes or longer evidence or reduced organ perfusion (lactic acidemia or 2 of the following: mental confusion, cyanosis of the extremities or sweating) and urine output less than 30 ml per hour. They found significantly lower cardiac output, stroke volume, mean arterial blood pressure and pulse pressure in the shock group. Heart rate central venous pressure and peripheral vascular resistance did not differ significantly. There was wide variation about the mean values and some of the cardiac outputs in the non-shock group were as low as some of the shock group. Normal peripheral vascular resistance was observed in 7 of the 16 shock patients. Calculated left ventricular stroke work resulted in fairly reliable separation of the shock and non-shock patients. Mean left ventricular stroke work was 26 ± 10 grammeter per beat in the shock group and 71 ± 22 grammeter per beat in the non-shock group. None of the 16 shock patients had a left ventricular stroke work in excess of 44 grammeter per beat, whereas only one of the non-shock patients had a left ventricular stroke work below 40 grammeter per beat. In the present study mean left ventricular stroke work was 21 grammeter per beat and the highest value was 4_ grammeter per beat, which corresponds very well with the findings of Swan et al.

Hamosh et al. (1969) compared the hemodynamic findings of 11 patients with uncomplicated AMI 8 patients with mild-moderate pulmonary congestion and AMI and 13 patients with shock and AMI. Central venous pressure was highest in the shock patients and cardiac index lowest. Left ventricular end diastolic pressures, however were highest in the group with mild-moderate congestion.

The low central venous pressures in 3 patients in the present study may be due to absolute or relative hypovolemia which is further discussed on page 33.

The inaccuracy of auscultatory or palpatory blood pressure measuring in shock syndromes of different genesis is widely accepted. This is even more important in shock associated with AMI where the diastolic pressure is critical for coronary perfusion and would be a guide for treatment. In the present series the systolic aortic pressure was higher than the palpable arterial pressure in all patients but one, and the diastolic pressure could not be obtained by auscultation in any patient.

Two patients (case AA and HJ) had normal systemic vascular resistance 15 units. They had central venous pressures of 8 and 9 mm Hg, and 16 and 11 mm Hg in pulmonary artery diastolic pressure, indicating adequate filling pressures for the right and left ventricle. Their heart rates were 114 and 110 per min., and their cardiac outputs 3.5 and 4.5 lit. per min. Yet, they had low arterial pressure and fulfilled the present criteria for shock (case HJ had a history of previous hypertension). Neither of them was among the CCU survivors.

There were 4 CCU survivors, 2 after treatment with volume expansion and after assisted circulation. Initially they did not have the highest cardiac outputs or the highest left ventricular stroke work. In fact, the one (case EB) with the lowest cardiac output, 1.0 lit. per min., is now still alive and fairly active 14 months afterwards.

When comparing the CCU survivors and non survivors no significant difference was found with regard to cardiac output, systemic vascular resistance, left ventricular stroke work, central venous pressure, pulmonary artery diastolic pressure and mean aortic pressure.

SUMMARY

Hemodynamic studies in 9 patients with shock complicating AMI generally showed a reduced cardiac output, stroke volume, aortic pressure and left ventricular stroke work. The heart rate, the central venous pressure, the pulmonary artery diastolic pressure and the systemic vascular resistance were generally elevated. However all parameters varied within wide ranges. No single hemodynamic parameter or combination of parameters could be found to be of prognostic value with regard to the CCU survival.

PART III
Volume loading

The use of infusions and transfusions in the trent ment of shock following AMI has been questioned. In recent years, however most reports have been encouraging (Allen et al. 1967 Nixon 1968 and Loeb et al. 1969)

None of the 9 patients studied hemodynamical ly (page 19) was given atropine sulphate or methyl scopolamine as their heart rate was above 80 per min. Seven were given a therapeutic trial with volume loading as first shock treatment. Left heart failure was considered a contraindication in the remaining two patients. Two of the 7 patients responded favourably to the test dose of 300 ml 5.5 per cent glucose rapidly infused intravenously and these two patients will be described clinically and hemodynamically The remaining 5 patients did not show any response in systolic blood pres sure or clinical symptoms, and they proceeded to further therapeutic attempts (page 35). All pa tients were routinely given sodium bicarbonate.

MATERIAL AND METHODS

The material has been described on page 19 above. The methods have been described on page 19 to 25

RESULTS

A. CLINICAL RESULTS

Case SA

A 67 year old man, previously in good health, was admitted following the onset of central chest pain. The ECG showed an acute anterior myocardial in farction. The first day was uneventful, and the fluid balance was ± 0 ml The second day alto- gether 30 mg frusemide was given because of basal pulmonary rales and moderate pulmonary congestion on chest X ray Yet, the fluid balance was +1300 ml. The systolic blood pressure was 110 to 140 mm Hg during these two days.

In the middle of the third day the blood pressure dropped to 75 mm Hg and the heart rate rose from 90 to 100 beats per min. Signs of cardio- genic shock appeared (mental confusion, cold, clammy skin with cyanosis of the ears and fingers and urine output 5 ml per hour)

While recording the central hemodynamics, 325 ml 5.5 per cent glucose was given in 23 min. (14 ml per min.) and shock symptoms disappeared. During the following 3 days, the blood pressure was between 85 and 110 mm Hg without any shock symptoms, and the fluid balance varied between +470 and +990 ml per day However during the 5th and 6th days his respiratory rate rose, arterial pO_2 fell to 60 mm Hg although 8 litres of oxygen per min. were given, and wide- spread pulmonary infiltrations developed on the chest X ray From the 6th day on he was treated in a respirator The blood pressure was 100 to 130 mm Hg and urine output normal until he had a sudden asystole on the 10th day

The autopsy revealed anterolateral myocardial infarcts which involved roughly 60 per cent of the left ventricle, without affecting the right ventricle. There were at least two infarcts of different ages, between 1 and 3 weeks, within the infarcted area, Hyaline membranes were seen in the pulmonary alveoli.

Case EP

A 51 year old man without previous cardiovascular disease. He was admitted because of repeated at tacks of central chest pain and observed in the CCU for 2 days without any evidence of AMI.

On the third day he was readmitted following recurring central chest pain and fainting. The ECG showed signs of an anterolateral infarction. He had not been treated with diuretics during the preceding 3 days in the hospital. Calculated fluid balance during these days was altogether +900 ml.

On the 4th day the patient had a systolic blood pressure fall to 70 to 80 mm Hg for 3 hours with oliguria, cyanosis, cold and clammy skin, mental confusion and metabolic acidosis. The heart rate was 110 beats per min. He was treated with rapid infusion of 300 ml 5.5 per cent glucose and 120 mE (200 ml) sodium bicarbonate. Shock symptoms then disappeared and for 10 hours his systolic blood pressure was between 85 and 100 mm Hg. Because of a high pulmonary artery diastolic pressure no more rapid infusion was given.

Ten hours later the blood pressure by palpation again dropped to 80 mm Hg for 1 hour and shock symptoms reappeared (oliguria, mental confusion, cold and clammy skin, cyanosis and metabolic acidosis). During recording of central hemodynamics, 1900 ml 5.5 per cent glucose was infused at rates varying from 4 to 14 ml per min during 6 hours. The shock symptoms disappeared and he was discharged from CCU 3 days afterwards.

On the 6th day following the infarction he developed dyspnea, rising respiratory rate, lowered arterial pO_2 (55 mm Hg in spite of 5.5 lit. of oxygen per min.) and scattered pulmonary infiltrates appeared on the chest X-ray. During respirator treatment from the 7th day on, the blood pressure was 100 to 120 mm Hg, the urine output normal and shock symptoms absent, but the arterial pO_2 continued to fall and he died on the 8th day.

At autopsy an anterior myocardial infarct was found involving roughly 55 per cent of the left ventricle. There was also 50 per cent involvement of the right ventricle. Several fresh peripheral pulmonary emboli and a pulmonary infarct (10 cm diameter) were seen. Microscopic examination revealed hyaline membranes in the pulmonary alveoli.

B. HEMODYNAMIC RESULTS

Case 5A

The results are shown in Table 11. During 23 min. 325 ml 5.5 per cent glucose, rate 14 ml per min., were infused. The central venous pressure rose from — to +6 mm Hg, the pulmonary artery diastolic pressure from 14 to 20 mm Hg and the aortic systolic pressure from 76 to 82 mm Hg. The cardiac output rose from 3.3 to 3.6 lit. per min. and stroke volume from 33 to 36 ml, the heart rate being constant. There was a slight eleva

Table 11. Case 5A. Hemodynamic findings during and after shock treated by volume loading

Day after infarction	5.5 % glucose infusion		Blood pressure Cuff	Aortic	CVP	PA_d	CO	SV	SVR	LVSW	HR	Rhythm	RR	Urine output
	ml	ml/min	mm Hg	mm Hg	mm Hg	mm Hg	l/min	ml	units	gm m/beat	min		/min	ml/hr
3[1]			70	76/5	—	14	3.3	33	1	25	100	AF	32	10
	3 5	14												
3[2]			85/	82/6.	6	20	3.6	36	18	27	100	AF	28	35
4			80/75	80/60	3	16	4.4	42	13	29	96	SR	30	35
5			100/80	114/8?	6	20	3.7	37	4	40	100	AF	3	100
5			95/80	110/80	6	20	4.1	41	20	45	100	AF	34	70

Abbreviations:

1) immediately prior to 5.5 per cent glucose
2) immediately after 325 ml 5.5 per cent glucose

CVP = central venous pressure
PA = pulmonary artery diastolic pressure
CO = cardiac output
SV = stroke volume
LVSW = left ventricular stroke work
SVR = systemic vascular resistance
HR = heart rate
SR = sinus rhythm
AF = atrial flutter
RR = respiratory rate

tion of the left ventricular stroke work and the systemic vascular resistance decreased. The urine output rose from 10 to 35 ml per hour

During the *following 3 days, the cardiac output* rose to finally 4 1 lit. per min., stroke volume to 41 ml and left ventricular stroke work to 45 gram meter per beat. The central venous pressure, the pulmonary artery diastolic pressure and the systemic vascular resistance remained unchanged.

Case EP

Volume loading was started with 5.5 per cent glucose at increasing infusion rates from 4 to 14 ml per min. During 6 hours altogether 1900 ml 5.5 per cent glucose were infused. As shown in Table 12 aortic systolic blood pressure rose from 110 to 116 mm Hg, the central venous pressure from *to 4 mm Hg and the pulmonary artery diastolic* pressure from 20 to 24 mm Hg. The cardiac output increased from 2.2 to 2.9 lit. per min. and the stroke volume from ?0 to .6 ml, the heart rate being essentially unchanged. Left ventricular stroke work rose and systemic vascular resistance decreased.

During the following days in the CCU the cardiac output rose to finally 5.3 lit. per min., stroke volume to 52 ml and left ventricular stroke work to 56 grammeter per beat. Central venous pressure remained constant (4 mm Hg) and pulmonary artery diastolic pressure decreased to finally 19 mm Hg. The systemic vascular resistance became normal (16 units).

COMMENTS

The use of infusions and transfusions in the treatment of shock following AMI has been much *disputed. Agress and Binder (1957) wrote: Intra*venous transfusions have served only to increase the mortality rate Much argument is devoted to the risk of producing pulmonary oedema in patients with obvious pump failure.

In the present series of 9 patients with shock due to AMI a test dose of 300 ml 5.5 per cent *glucose was given to 7 patients and was followed* by frank pulmonary oedema in one patient (case AM). However this coincided with an abrupt change from sinus rhythm to atrial fibrillation, frequency 170 beats per min. and was therefore most probably not a complication to the volume loading.

In recent years several authors have reported on encouraging results from infusion therapy in shock due to AMI. Nixon (1968) treated 11 consecutive

Tabl 12 Case EP Hemodynamic findings prior to during and after shock treated by volume loading

Day after infarction	5 5 % glucose infusion		Blood pressure		CVP	PA_d	CO	SV	SVR	LVSW	HR	Rhythm	RR	Urine output
			Cuff	Aortic										
	ml	ml/min	mm Hg	mm Hg	mm Hg	mm Hg	l/min	ml	units	gm m/beat	/min.		/min.	ml/hr
1			100/70	110/80	2	17	2.6	24	38	27	108	SR	20	20
2			80/?	110/80	0	21	3.0	28	30	32	108	SR	24	20
2[1])			85/?	110/80	2	20	2.2	20	43	23	110	SR	24	12
	600	4—11												
2			100/?	118/84	4	22	2.8	26	34	30	108	SR	22	65
	400	7—14												
			115/80	122/86	4	4	2.6	23	37	25	110	SR	22	110
	900	6—13												
2[2])			110/80	116/80	4	4	2.9	26	32	29	112	SR	20	155
			110/90	110/76	4	4	3.2	29	26	28	109	SR	18	40
3			90/70	100/70	4	18	3 4	30	21	30	114	SR	20	50
3			95/70	96/68	4		3 2	23	20		140	AF	20	30
4			110/60	110/70	4	19	5.3	52	16	56	100	SR	16	65

Abbreviations:
1) immediately prior to 5 5 per cent glucose
2) immediately after 1900 ml 5 5 per cent glucose
Remaining abbreviations, see Table 11

patients with AMI and shock by infusion of 5 per cent dextrose ranging from 50 to 200 ml at a time. Each dextrose administration raised the arterial and central venous pressures. Seven patients were saved and in no instance did frank pulmonary oedema arise. In the 4 patients who died, the central venous pressure rose but the arterial pressure failed to increase. In some patients Nixon and colleagues (Nixon et al. 1966 and Nixon 1968) found that arterial pressure, peripheral circulation and urine flow were restored after infusion treatment in spite of an initially high central venous pressure.

Cohn and colleagues (1967) studied the hemodynamic effect of low molecular weight dextran in 9 patients with AMI and shock. Central venous pressure rose 1 to 8 mm Hg in all patients. Arterial pressure rose in 7 of these 9 patients and the cardiac output in 8. Left ventricular stroke work rose in all but one patient. Three of the 9 patients had systolic blood pressures over 120 mm Hg prior to dextran infusion.

Allen et al. (1967) gave different therapies to 30 patients with shock due to AMI. Six patients without signs of pulmonary congestion responded favourably after a test dose of 100 to 300 ml 5 per cent dextrose in water over a period of 5 to 15 min. They were then treated with infusion of large volumes of this 5 per cent dextrose solution (120 to 300 ml per hour). All 6 survived. They had central venous pressures below 10 cm water before treatment, and after it a prompt rise in systolic arterial blood pressure (average increase 37 mm Hg at 4 hours) and urine output was noticed without alteration of the venous pressures. Of the remaining 24 patients only 7 survived after other forms of treatment.

Loeb and colleagues (1969) used low molecular weight dextran as a plasma volume expander. Twelve patients with clinical features of shock following AMI were given an average of 580 ml (range 300 to 1000 ml) low molecular weight dextran at mean infusion rate of 7.6 ml per min. Two patient had elevated central venous pressures and in neither was any clinical or hemodynamic improvement seen. The remaining 10 patients had central venous pressures below 7 mm Hg and 5 of these survived. Increased arterial pressure, cardiac index and an average increase in central venous pressure of 1.0 mm Hg per 100 ml dextran infused was noted in the survivors. In the 5 non-survivors the central venous pressure rose 1.9 mm Hg per 100 ml dextran infused and no increase in arterial pressure or cardiac index was observed.

Lindén (1964) gave low molecular weight dextran to 48 patients with AMI. The mortality was 15 per cent and was significantly lower than the 33 per cent in a control group of 235 patients. There was no conclusion whether this was due to a lower incidence of shock.

Langsjoen et al. (1968) treated a randomized number of patients with AMI by infusion of 10 per cent low molecular weight dextran in 5 per cent glucose (500 ml in the first 4 hours, then 500 ml every 8 hours). The mortality in this group was 13.3 per cent which was significantly lower than the 3..3 per cent mortality of the control group. The dextran-group had 9 per cent shock and the control group 17 per cent. However the authors could not conclude whether the improved mortality was the result of rheologic factors or a beneficial effect on shock from increased plasma volume.

It seems plausible that at least some patients with shock due to AMI may respond favourably to infusion therapy especially among those with absolute or relative hypovolemia. Allen et al. (1967) reported on a 20 per cent incidence of relative hypovolemia (defined as a slight or no increase in right atrial pressure after a test volume load of 100 to 300 ml 5 per cent dextrose in water infused in 5 to 15 min.) in patients with AMI complicated by shock. As this condition may be successfully treated, it is important to recognize it, the central venous pressure being a valuable guide.

The two patients in the present study differed somewhat from each other in their reaction to infusion therapy. In the first patient (case 5A), the central venous pressure rose by 8 mm Hg, from —. to +6 mm Hg, after only 3.5 ml 5.5 per cent glucose. The pulmonary artery diastolic pressure

simultaneously rose from 14 to 20 mm Hg (43 per cent). In the other patient the central venous pressure increased only 2 mm Hg, from 2 to 4 mm Hg, although he was given as much as 1900 ml 5.5 per cent glucose with as fast an infusion rate. During the same time, his pulmonary artery diastolic pressure rose from 20 to 22 mm Hg (10 per cent). It may therefore be important not only to find the hypovolemic patients by way of central venous catheterization but also to guide the infusion therapy response by the pulmonary artery pressure rather then giving fixed volumes of fluid.

The cause of hypovolemia in shock due to AMI is still not explained. Whether it is an absolute hypovolemia due to diffusion of plasma into the extravascular space, excessive sweating or urine production, vomiting, or the use of diuretics, or a relative hypovolemia due to dilatation of the venous vascular bed is not definitely established. Some authors have found the blood volumes to be normal or only slightly reduced in shock secondary to AMI (Agress et al. 1950, Fries et al. 195? and Smith et al. 1954). The two patients in the present series had been observed in hospital a few days before shock intervened and both had positive fluid balance during this period (although case SA had had 30 mg frusemide 2 days prior to shock). No one was excessively sweating or vomiting.

SUMMARY

Seven patients with shock due to AMI were treated with a test loading of 300 ml 5.5 per cent glucose by intravenous infusion. Two of them responded favourably and their clinical and hemodynamic course was studied. During therapy aortic, central venous and pulmonary artery diastolic pressure rose as did also cardiac output and left ventricular stroke work. The systemic vascular resistance declined. Both patients recovered from shock soon after treatment had started and could be discharged from the CCU. However they died some days later with progressive hypoxemia, and at autopsy the lungs showed protein deposits (hyaline membranes)

PART IV
Intra-aortic balloon pumping

Several different forms of temporary assisted cir culation have been applied in shock following AMI and some of these have been used clinically The different methods have recently been sur veyed by Sanders et al. (1971). Some techniques are based on the principle of diastolic aortic agu mentation (Clauss et al. 1961 Moulopoulos et al. 196.., Ruiz et al. 1968 and Arntzenius et al. 1969). A limitation to the use of part of these pumps is the resulting hemolysis of the blood which is pumped through the aortic tubes However this problem was overcome when Clauss et al. (196..) and Moulopoulos et al. (1962) introduced the intra aortic phase-shift balloon pump technique Since then different types of balloons and pumps have been used (Kantrowitz et al. 1968a, Bregman et al. 1971 and Dunkman et al. 1971). Monosegmented and serially inflated multisegmented balloons were *compared experimentally by Chatterjee and Rosen* sweig (1971). They found optimal haemodynamic effects with monosegmented balloons which are just subocclusive.

Recently some reports of clinical trials with intra-aortic phase-shift balloon pumping have been published However when planning this study in 1969 the most positive clinical results had been published by Kantrowitz et al. (1968a). Fifteen patients in terminal shock due to AMI were treated and in 14 of these the shock was reversed. Six patient were long term survivors. This method was therefore chosen for the present study using a monosegmented subocclusive balloon.

MATERIAL AND METHODS

Seven f the 9 patients (page 19) were not treated with or did not respond to volume loading. In one of these cases (HJ) intra-aortic balloon pumping (IABP) was considered contraindicated as the pa tient had a history of severe heart failure (function group IV New York Heart Association). Prepara tions for IABP were made in the remaining 6 patients who during this period were treated with infusions of sodium bicarbonate and isoproterenol as required. One patient (case MK) died before the intra-aortic balloon catheter had been inserted. Thus 5 patients were treated with IABP and during as well as after this treatment studied clinically and hemodynamically

An intra-aortic balloon catheter was also in serted but not used in another patient, who how ever recovered from shock following repeated volume loading (case EP). Thus, altogether 6 pa tients had an intra-aortic balloon catheter inserted (Table 13).

The insertion of the balloon catheter was per formed at the bedside in the CCU The balloon catheter was advanced from the right femoral artery in all patients. After local anaesthesia with 15 to 20 ml 0.5 per cent mepivacain. chloride (Carbocain® Bofors, Mölndal, Sweden) the femo-ral artery was dissected free 5 to 7 cm below the inguinal ligament and a 1 cm long arteriotomy was then performed on the anterior surface of the superficial femoral artery A Fogarthy catheter (F 4 or 5 Stille Werner Stockholm, Sweden) was advanced into the aorta above the bifurcation and drawn back inflated. The balloon catheter (Milton Roy Company St. Petersburg, Florida, USA), stif fened by a stylet and with the balloon deflated and wrinkled around the catheter end, was intro-duced through the arteriotomy and advanced to the decending part of the thoracic aorta. Ideally it

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Table 13 Age sex and clinical findings in 6 patients submitted for intra-aortic balloon counterpulsation (IABP)

Case	Age	Sex	Body surface area	Previous myocardial infarction	ECG site of the acute infarction	Time from onset of symptoms to shock	Duration of surgery	Time from shock to start of IABP	Palpable blood pressure	Aortic blood pressure	Mental confusion or unconsciousness	Cyanosis	Urine output	Base excess	IABP	Time in shock	Total time with intra-aortic balloon	Balloon catheter withdrawn in vivo	CCU survival time after onset of shock	CCU survival
			m²	No		hrs	min.	hrs	mm Hg	mm Hg			ml/hr	mE/lit.	hrs	hrs	hrs		hrs	
AM	74	M	1.84	1	L1	s	30	5**	60	60/44	+	+	0	—10	68	21	85	+	97	+
EB	71	M	1.82	1	L	67	45	3	u	62/43	+	+	5	— 4	90	23	120	+	157	+ **
SR	59	M	1 79	0	L1	s	35	2*	u	60/44	+	+	0	— 6	41	37	41	—	43	—
AA	67	M	1.87	1	a.	s	25	3**	u	54/40	+	+	0	—12	17	8	17	—	20	—
EH	58	M	1.90	0	L1	5	20	1	90	99/74	+	+	0	— 8	80	1	80	—	83	—
EP	51	M	_09	0	a.1	20	20	—	75	100/80	+	+	10	— 8	—	3	50	+	78	+

Abbreviations:
a. = anterior
a.l. = anterolateral
L = inferior
LL = inferolateral
= shock on admission
u = unobtainable
= operation on both femoral arteries
= time from admission
** = alive 14 months afterwards

should be placed with the tip just distal to the left subclavian artery. This was made without fluoroscopic control according to measurements before the insertion, and the position was later controlled by a chest X ray.

At autopsies it had been found that the length of a stretched catheter from the femoral arteriotomy to the medial end of the clavicle outside the patient's body equaled the distance from the arteriotomy through the aorta to the ideal position just below the left subclavian artery.

Prior to the introduction of the balloon catheter 4000 units of heparine were given intravenously and heparinization was continued with 15000 to 20000 units per 24 hours in 6 doses. Therapy was controlled by estimations of bleeding time and coagulation time.

As soon as the balloon catheter had been placed in a suitable position, sterile tubing from the driving unit was connected to the free catheter end so that assisted circulation could be started without waiting for closure of the incision. A 10 mm arterial Dacron graft was then sutured end to side to the arteriotomy and the other end of the graft tied around the catheter with snare according to the technique described by Kantrowitz and associates (1968b). The suturing was checked for any bleeding and the wound closed. The catheter was carefully fixed with tape to the patient's leg. The bleeding during the procedure was approximately 200 ml.

The overall catheter length was 70 cm and the length of the inflatable element 15 cm. The diameter of the catheter was 5 mm and of the fully inflated balloon 18 mm. The balloon displacement when expanded was 32 ml. The monosegmented balloon was made of polyurethane and safe up to a pressure of 700 mm Hg.

The driving unit (Kantrowitz phase shift balloon pump system, Milton Roy Company, St. Petersburg, Florida, USA) was connected by a plastic tubing to a helium source, which was adjusted to 20 to 25 Psi. The helium pressure of the driving unit was adjusted to 90 to 180 mm Hg. If the pressure rose above 200 mm Hg the balloon was vented to the atmosphere.

The ECG signal (approximately lead CR_1) was derived from the patient oscilloscope and fed into the driving unit. The signal was amplified so that the pump unit was trigged by the R-wave. The

onset of inflation could be adjusted by use of a "delay" knob of the driving unit. The setting was made so that the aortic pressure increase caused by the ballon inflation started slightly after the dicrotic notch of the aortic pressure curve. The onset of deflation of the balloon was adjusted by a "balloon inflated" knob so that the balloon effect on the aortic pressure terminated slightly before the next systolic upstroke in the aortic pressure curve. By recording the inflation-deflation signal together with the ECG and aortic pressure at a paper speed of 100 mm per second, approximate settings could be made without pumping. In this way the risk of inflating the balloon during systole was minimized.

After these adjustments the pump was turned on and paper tracings at 100 mm per second were obtained with the pump on and off for a few heart beats at a time allowing for fine adjustments of time settings until correct timing was achieved. This was considered, when the pressure wave of the balloon inflation started at the upstroke of the dicrotic notch and terminated at the starting point of next systolic upstroke. The fine adjustments were repeated several times a day.

The delay, i.e. the time from the R-wave to initiation of inflation could be varied between 50 and 1050 milliseconds. The time from inflation to deflation of the balloon had a range from 100 to 1100 milliseconds. Premature beats immediately terminated the inflation, and deflation took place.

Extraction of the balloon was performed under local anaesthesia. The snare around the catheter was untied and the catheter drawn out. An inflated Forgarthy catheter was drawn back both proximally and distally from the arteriotomy. The graft was cut off to appropriate length and sutured over the incision forming a patch over the arteriotomy.

Throughout the period of IABP the pressures were generally recorded every 2nd hour and cardiac output determined at varying intervals at least 4 times a day. The measurements were obtained with the pump both on and off. The pump off pressures were usually recorded about 4 min. following interruption of IABP. The pump off determinations of cardiac output were usually performed 5 to 15 min. after discontinuing IABP.

RESULTS

A. TECHNICAL RESULTS

One patient (case EB) had the left femoral artery first operated upon, but the balloon catheter could not pass beyond the iliac artery. The right femoral artery was then successfully used. In all the other patients the right superficial femoral artery was directly used successfully. Arteriosclerotic plaques had to be removed in one patient and dilation of an arteriosclerotic stenosis had to be performed in one patient before the balloon catheter could be inserted into the superficial femoral artery. When advanced, the catheter was stopped some 15 to 20 cm from the arteriotomy in 3 patients. Even when rotated it was not possible to pass through. A Forgarthy catheter was then advanced to dilate the stenosis. After this procedure the balloon catheter could be passed in these 3 patients.

The mean time from start of operation until assisted circulation could be instituted was 30 min., range 20 to 45 min. The longest time included the operation of both right and left femoral arteries. The time from admission or shock until the balloon was in position for pumping was 1 1/3 mean 3 hours. Three of the 6 patients were in shock already when first seen. The other 3 patients developed shock in the CCU and the time interval from onset of shock until the balloon was in position was 1 to 3 hours, mean 2 hours.

The position of the balloon catheter was controlled by chest X-ray and found to be adequate in all patients. In one patient (case AM) the balloon catheter was displaced into the abdominal aorta on one occasion due to the patient moving in the bed. The catheter could easily be put back into the thoracic aorta. Used or not the balloon catheters remained in the aorta of the 6 patients from 17 to 120, mean 66 hours.

The balloon catheter was extracted in vivo without any complications in 3 patients brought out of shock. However in one of these (case EP) no IABP had been performed. In the two patients who recovered from shock after assisted circula-

tion, the balloon catheter was left in place for another 17 and 30 hours after termination of counterpulsation. No balloon catheter showed any damage. No wound infection was seen in any patient. G penicillin (2 g intramuscularly per 4 hours) had been given prophylactically

Autopsy findings
Six patients were autopsied. The aorta was inspected and was found to have a thin thrombotic string (diameter 1 to _ mm, length 10 to 20 cm) along the catheter in all patients. It was losely attached to the aortic wall and thread like thin in every case. There were no hemorrhages in the arterial or aortic wall. The balloon catheter showed no damage in any case.

COMMENTS

It has been suggested that the use of the IABP method might be limited by arteriosclerotic changes of the femoral arteries. In the present series of 6 patients the catheter could, however be correctly placed in the thoracic aorta in all instances although the mean age of the patients was as high as 63 years. In none of these 6 patients was it necessary to extract the catheter because of circulatory insufficiency of the leg. Bregman et al. (1971) reported on 5 patients with shock due to acute myocardial infarction treated with dual chambered intra-aortic balloon assist. The mean age was 60 years (range 44 to 76). Eight other patients met the criteria for assisted circulation, but 6 of these died before assistance could be instituted and in patients with aortic iliac disease, the balloon could not be inserted.

In a recent series of 12 patients submitted for IABP Mueller et al. (1971) reported of the death of one patient, directly attributed to rupture of the balloon after 36 hours of counterpulsation. Furman et al (1971) showed that helium from rupture of an intra-aortic balloon caused death almost instantaneously in experimental animals. Turner and colleagues (1966) reported 100 cineangiocardiographic studies utilizing 50 ml of intravenously injected carbon dioxide with no morbidity Carbon dioxide has therefore been claimed to be safer for use in intra aortic balloons (Bregmen et al. 1971).

In the series of Mueller et al. (1971), 12 patients with a mean age of 63 years, there was one patient who developed severe ischemia of the lower extremity distal to the site of balloon insertion and one patient in whom the ballon could not be inserted because of severe occlusive disease of both femoral arteries.

Buckley et al. (1970) treated 8 patients with IABP using a threesegmented balloon. No peripheral emboli were diagnosed during life in any patient. Three patients survived counterpulsation and no one showed vascular insufficiency in the catheterized leg. Post mortem examination was performed on 4 of the 7 patients who died. No gross injury to the aorta related to balloon pumping was found. Microscopic sections of the descending aorta showed small focal areas of endothelial disruption in one case.

B CLINICAL RESULTS

Five patients were treated with IABP All were men, and the mean age was 66 years, range 58 to 74 years. The mean time in shock until start of assisted circulation was 3 hours, range 1 to 5 hours. The mean time in shock was 20 hours, ranging from 8 to 37 hours. Assisted circulation was given during 17 to 90 mean 59 hours.

Shock was reversed in all patients and in 2 of them (case AM and EB) the balloon catheter could be withdrawn 17 and 30 hours after termination of assisted circulation. Both stayed in the CCU for 29 and 67 hours after IABP had been stopped and were then discharged from the CCU Case AM died one day after discharge from the CCU but case EB is still alive and healthy 14 months afterwards.

Effect of IABP on clinical symptoms
The first change of clinical symptoms observed concerned the degree of consciousness. Two patients were unconscious (case AM and EB) and after one hour of assisted circulation they were mentally alert. The same quick effect was observed in the rest of the patients, whose sensorium was blurred before counterpulsation was intiated. Blood pressure on palpation was unobtainable in 3

patients and after 1 to 20, mean 9 hours of assisted circulation it could be measured again. Cyanosis and peripheral coldness disappeared in all patients. Urine flow started again in all patients, after 1 to 25 means 1_ hours. There was no gross tendency to acidosis during the IABP and the first bicarbonate infusion was given after 5 to 93, mean 38 hours of circulatory assistance. Hemoglobin concentrations fell in all patients but one, and the fall was much greater than could be explained from the bleeding during the arteriotomy. Haptoglobin values did not indicate any hemolysis of clinical significance.

Case reports

Case AM

A man, 74 years old, with one small myocardial infarction 7 years previously. On admission, because of persisting central chest pain, the patient was in deep shock with a blood pressure of 80 mm Hg, general cyanosis, peripheral coldness, mental confusion and oliguria. The ECG showed signs of acute inferolateral myocardial infarction. The respiratory rate was 34 per min., urine output 8 ml during the first hour, arterial pO_2 50 mm Hg in spite of added oxygen and the base excess —10 mE per lit. During insertion of the catheters he was treated with 300 ml 5.5 per cent glucose, sodium bicarbonate and isoprenaline infusion (2.8 microgram per min. during 3 hours). The blood pressure rose to 100 mm Hg for one hour but all other shock symptoms remained. There was one episode of atrial fibrillation and frank pulmonary oedema developed.

After this hour the blood pressure fell to 60 mm Hg and assisted circulation was started 6 hours after admission to the CCU and continued for 68 hours. Occlusion of the intra-aortic balloon was at one instance suspected and a trial with nor-epinephrine infusion (8 microgram per min. during 6 hours) was then made without effect on the blood pressure, urine output or clinical symptoms. The pressure curve form slowly altered towards normal during the 6 hour period.

After one hour of assisted circulation the patient became mentally alert, the cyanosis and coldness disappeared but the anuria continued for another 20 hours. Besides heparin and penicillin, no other therapy was given until the third day when atrial fibrillation (ventricular rate 100 per min.) again intervened and was treated with 0.7 mg strophantidine and 20 mg frusemide. Ten hours later a DC electroconversion was successfully performed and the circulatory assistance was stopped after another _ hours. The systolic blood pressure rose to 160 mm Hg and after another 17 hours the balloon catheter was extracted and the patient discharged from the CCU.

Towards the end of the 4th day the blood pressure started to fall and the heart rate to rise. There was diarrhoea with considerable amount of blood. Low molecular weight dextran and blood was given. Ten hours later on he died from circulatory standstill while an attempt was made to pass a gastric tube.

Autopsy revealed a one week old inferolateral infarct, 30 per cent of the left ventricle, with tamponade caused by a 1 mm wide rupture of the free left ventricular wall. There was also a 5 per cent old fibrosed infarct in the posterior wall. A fresh duodenal ulcer and large amounts of intestinal blood were seen. No hyaline membranes of the pulmonary alveoli were found.

Case AM	Day 1	Da	Day 3	Day 4	Day 5
Shock	——				
Counterpulsation	——	——			
Hemoglobin, g 100 ml	15.6	12.7	10.4	10.3	10.6
Haptoglobin, mg 100 ml		11	128		174
Creatinine, mg 100 ml		3.8			9.5
Fluid balance	+1500	+300	+100	+700	+2200

Case EB

A man, 71 years old, with a history of bleeding ulcer, hypertension and myocardial infarction. He was referred from another hospital on the third day following an acute inferior infarction with complete heart block and hypotension. Although transvenous cardiac pacing was immediately started with a rate of 90 beats per min.,

Case EB	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Shock			———	———				
Counterpulsation								
Hemoglobin, g/100 ml	14.2			10.8	10.9	10.4	9.3	9.7
Haptoglobin, mg/100 ml					74	300	232	284
Creatinine, mg/100 ml		1.6	1.7	2.8	3.7		9.5	9.9
Fluid balance				+1000	+200	+200	+1100	+300

the blood pressure continued to fall to 50 mm Hg. Within one hour the patient was semiconscious, cyanotic, acidotic and oliguric. No effect on blood pressure or clinical shock symptoms were obtained by rapid infusion of 300 ml 5.5 per cent glucose in 10 minutes, sodium bicarbonate and isoproterenol (2.8 microgram per min. during [illegible] hours). The patient was unconscious and the blood pressure could not be obtained by palpation when assisted circulation could be started 3 hours after the onset shock. IABP was continued for 90 hours until the 4th day after the onset of shock. The patient was hemodynamically followed for another 29 hours before the balloon catheter was withdrawn on the 6th day after the onset of shock.

After one hour of assisted circulation the patient became conscious and cyanosis and peripheral coldness disappeared. Without assisted circulation his blood pressure was unobtainable by palpation for 20 hours and he was oliguric for 3[illegible] hours. Besides heparin and penicillin the patient was treated with lignocaine 2 mg per minute because of few hours of ventricular tachycardia, sodium bicarbonate in a total amount of [illegible]40 mE and also antacids as prophylaxis against gastric ulcer. A blood loss of about 500 ml in association with the bilateral femoral arteriotomy was compensated with infusion of 800 ml blood. From the 6th da[illegible] on, frusemide was given because of signs of moderate pulmonary congestion.

On the 7th day after infarction, when still paced because of complete heart block, the patient had 5 long attacks of rapid ventricular tachycardia with loss of consciousness possibly caused by dislocation of the pacemaker electrode. On the 8th day the patient was in sinus rhythm with A V block I and was discharged from the CCU with a systolic blood pressure of 130 mm Hg.

The patient remained in hospital for 3 months because of right and left sided heart failure, a minor stroke possibly caused by an embolus and some attacks of ventricular tachycardia which required DC electroconversion. Fourteen months after his cardiogenic shock he is in good condition and at his routine check-ups there have been no physical signs of congestive heart failure but slight lack of coordination in his right arm and leg. Mentally he is in a very good condition. The serum creatinine is 1.5 mg per 100 ml and the ECG shows regular sinus rhythm with A V block I

Case SR

This man was 59 years old and previously healthy. He was admitted because of central chest pain for 10 hours. On admission the blood pressure was 75 mm Hg and the patient had mental confusion, peripheral cyanosis, cold clammy skin, anuria and metabolic acidosis. The ECG showed an acute inferolateral myocardial infarction. Rapid infusion of 300 ml 5.5 per cent glucose together with sodium bicarbonate had no effect on shock symptoms. Assisted circulation was started 2 hours after admission. Three hours later

Case SR	Day 1	Day	Day 3
Shock	———	———	
Counterpulsation			
Hemoglobin, g/100 ml	15.8	15.5	11.0
Haptoglobin, mg/100 ml		192	
Creatinine, mg/100 ml		3.1	3.5
Fluid balance	+1700	+900	+700

the patient was mentally alert and the shock symptoms had disappeared. Treatment included heparin, sodium bicarbonate, frusemide, antacids and mild sedatives. Nor-epinephrine infusion (8 microgram per min. during 27 min., was given on one occasion because of suspicion of balloon occlusion but no hemodynamic or clinical effects were seen. The central venous pressure was elevated *from 0 to 8* mm Hg *by* 200 ml *low molecular weight dextran, but it had no effect on* aortic blood pressure. At the end of the first day the palpatory blood pressure was 90 mm Hg with circulatory support.

The arterial pO_2 declined and the respiratory rate rose progressively and the patient complained of increasing dyspnea. He was therefore treated by a respirator 24 hours after admission.

Although still hypotensive during the second day there were no shock symptoms, and the urine output was adequate. After 41 hours of assisted circulation the patient died in sudden asystole.

At autopsy a myocardial infarct, 6 to 10 days of age, was found extending through the free left ventricular wall. In the ventricular septum there was a one to two days old infarct. The *first infarct involved roughly 70* and *the latter* 30 *per cent of the left ventricle. Ten per cent* of the right ventricle was also involved. Massive interstitial oedema of the pulmonary alveoli was found but no hyaline membranes.

Case AA

This man was 67 years old and had experienced one myocardial infarction 21 years previously. He was admitted to another hospital because *of central chest pain for a few hours.* He was referred to this CCU 15 hours later with a blood pressure of 85 mm Hg, cyanosis, mental confusion, metabolic acidosis and anuria. Sodium bicarbonate and 5.5 per cent glucose were rapidly infused without any effect on blood pressure or clinical symptoms. After 2 hours the blood pressure was palpatory unmeasurable and 30 minutes later on assisted circulation was started.

After one hour of assisted circulation the patient became normotensive, *mentally* alert and the

Case AA	Day 1	Day 2
Shock	—	
Counterpulsation	—	—
Hemoglobin, g/100 ml	16.2	15.3
Fluid balance	+[illegible]	+1000

cyanosis and skin coldness disappeared completely Heparin, penicillin, lignocaine, frusemide, antacids and sedatives were given. After 14 hours, several periods of complete A-V block and asystole appeared. A transvenous pacemaker electrode was inserted into the right ventricle but there was a progressive decline in blood pressure until he died *5 hours later after a total of 17 hours of IABP*

At autopsy an old infarct of the inferior wall was found. An about one week old infarct involving the rest of the inferior wall and the lateral wall and an about 3 days old infarct of the anterior wall were also found. Altogether about 100 per cent of the left ventricle was infarcted. Interstitial oedema of the pulmonary alveoli was present but no signs of hyaline membranes.

Case EH

This 58 years old man was previously healthy and was admitted because of central chest pain for 3 hours. The ECG showed signs of an acute inferolateral myocardial infarction. After 2 hours the blood pressure fell to 50 mm Hg, and the patient became semiconscious, developed peripheral cyanosis, metabolic acidosis and anuria. He *was treated with* 200 *ml of 5.5 per cent glucose* and sodium bicarbonate *with no effect on the* shock symptoms. The respiratory *rate rose* and pulmonary odema developed. Intra-aortic balloon pumping was started one hour after the onset of shock.

During the first hour of assisted circulation the blood pressure rose to 90 mg Hg and the shock symptoms disappeared. Urine flow became normal. Therapy included heparin, penicillin, frusemide, antacids and sedatives. During the first 3 days intermittent atrial fibrillation occurred with high ventricular rates and was treated with digitalis,

Case EH	Day 1	Day 2	Day 3	Day 4
Shock	———			
Counterpulsation				
Hemoglobin, g/100 ml	14.0	13.0	11.2	9.1
Haptoglobin, mg/100 ml		110		
Creatinine, mg/100 ml		1.8	1.4	1.2
Fluid balance	—900	—900	—1400	

frusemide and quinidine. From the 4th day the blood pressure progressively declined and the patient became anuric. However he still was mentally alert and no other shock symptoms appeared. He died in frank pulmonary oedema and terminal ventricular fibrillation after 80 hours of assisted circulation.

At autopsy a one week old transmural inferolateral infarct (roughly 35 per cent of the left ventricle) and an about 3 days old subendocardial anterolateral infarct (15 per cent) were found. Altogether 50 per cent of the left ventricle was infarcted. Hyaline membranes were evident in the pulmonary alveoli.

COMMENTS

Only a few reports on the clinical effect of IABP in shock secondary to AMI have been published (Summers et al. 1969 Bregman et al. 1971 Dunkman et al. 1971 Krakauer et al. 1971 and Mueller et al. 1971) Summers et al. (1969) treated 3 patients by IABP using a 33 ml volume balloon. Their shock criteria were essentially the same as in the present study Counterpulsation was started after inadequate response to pharmacologic treatment and volume replacement and was continued for 3 7 and 9 hours. Each patient had severe obstructive triplevessel coronary artery disease on selective coronary angiography and the left ventricles were large and contracted poorly Although marked improvement in pressure, flow and metabolic factors occurred, no patient survived.

Bregman et al (1971) treated 5 patients in shock secondary to AMI by use of dual-chambered balloon. The time interval from onset of shock to initiation of IABP was 31 hours. All patients had pulmonary oedema prior to the circulatory assist, and within 30 minutes of IABP all had clear chests, both by auscultation and roentgenography Two patients were comatose and two had clouded sensoria prior to the assist. Within 30 min. of pumping all became alert. Four patients were anuric and one oliguric prior to assisted circulation. At the termination of IABP 3 of them had normal urine output. Assisted circulation was given from 4 to 16, mean 12 hours. Four patients survived the assistance procedure However only one patient was alive and well after 1½ years. One patient died suddenly as a result of extension of the infarct into the septum, one patient died after 2 days of pneumonia and renal failure, one patient died after 7 days from ventricular rupture and cardiac tamponade and the fourth patient died from intractable left ventricular failure.

Dunkman et al. (1971) used a three-segmented intra-aortic balloon after a trial with pharmacological therapy in 39 patients with shock complicating AMI. The average time from development of shock to institution of counterpulsation was 14 hours in 31 patients and 3 to 9 days in 7 patients. The shock syndrome was reversed in 31 patients. *Five of 26 patients treated with IABP* alone survived. Thirteen patients judged unable to survive off assisted circulation were operated on for emergency revascularization and/or infarctectomy with counterpulsation continuing during preoperative angiography as well as postoperatively Five survived and were alive after 2 to 10 months.

Krakauer et al. (1971) treated 30 patients with shock due to AMI by use of a nonocclusive monosegmented intra-aortic balloon. Different results were obtained in the 20 patients with "early" shock (shock within 12 hours after onset of symptoms) and the 10 patients with "delayed" shock (shock which developed after 30 hours). Shock was reversed in 90 and 70 per cent respectively Nine patients (45 per cent) of the "early" shock group were long term survivors compared with none of the "delayed" shock group. One patient of the "early" group and 6 patients of the "delayed" group had myocardial rupture.

Mueller et al. (1971) treated 12 patients in shock complicating AMI with IABP. They used a monosegmented intra-aortic balloon. One patient was alive 21 months afterwards. Four of the other 11 patients lived for 3 to 21 days after termination of assisted circulation. Postmortem examinations in 6 of the 11 patients who died revealed extensive old and recent myocardial infarctions associated with severe coronary artery disease.

Volume loading or IABP brought 7 of 9 patients out of shock in the present series. Two of them left the intensive care area and one is still alive one year later. During the study period 8 patients with shock complicating AMI were treated in the CCU when the shock team was unavailable. In only one of these patients could shock be reversed ($P < 0.01$) and none left hospital alive. However, the long term result was poor also in the group treated with volume loading or IABP. The main causes of death were extensive infarcts and respiratory failure.

Three patients (case SA, EP and SR) had respiratory failure and were treated by respirator. Two of these at autopsy showed hyaline membranes of the pulmonary alveoli. However during the period 1968 to 1970, 3 patients with shock complicating AMI not treated in respirator also showed hyaline membranes at autopsy. Respirator treatment per se does therefore not seem to be the only cause of this complication.

Altogether 3 patients of the present study showed hyaline membranes and their survival time following onset of shock was 4 to 7, mean 6 days, while it was 1 to 6, mean 3 days for the patients without protein deposits in the lungs. A prolonged survival time after shock complicating AMI may increase the incidence of shock lung. The genesis of this syndrome is still unsettled according to a recent survey by Kamada and Smith (1972).

The only possible way to act against extensive infarcts and shock lungs seems to be prophylactic treatment of predicted shock.

C. HEMODYNAMIC RESULTS

Comparison of pump off and on. Mean of all estimations during the whole period of IABP

The hemodynamic results for each patient are given in Table 14 to 18 and for all patients together in Table 19 and Fig. 12.

Aortic pressures

When initiating the IABP the aortic pressure curve changed as shown in Fig. 11. With the pump on the aortic systolic pressure declined by 8 to 16, mean 13 per cent of the pump off value.

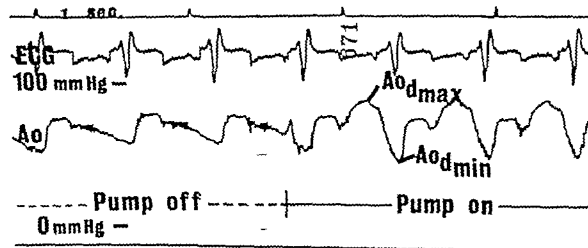


Fig. 11. Aortic pressure curve (Ao) recorded during pump off and pump on (IABP).

Ao_{dmax} = maximal aortic diastolic pressure
Ao_{dmin} = minimal aortic diastolic pressure

Table 14 Hemodynamic effect of IABP in case AM Mean of all estimations during th 68 hour period of assistance

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm H	mm Hg	mm Hg	mm Hg	l/min.	ml	units	gm m/beat	mm Hg beat/min.
Pump off	91	79	71	57	64	66	29	13	13	3 6	36	16	37	9100
Pump on	76	65	91	46	75	71	29	13	13	3 9	40	16	32	7500
Difference	—15	—14	+20	—11	+11	+5	0	0	0	+0.3	+4	0	—5	—1600
Difference in per cent f pump off value	—16	—18	+28	—19	+17	+8	0	0	0	+8	+11	0	—14	—18
P	<0.001	<0 001	<0 001	<0.001	<0.001	N.S.	N.S	N.S.	N.S.	N S	N.S.	N.S.	N.S.	<0 001

Abbreviations:

Ao = aortic systolic pressure
Ao_{ms} = aortic mean systolic pressure
$Ao_{d\,max}$ = maximal aortic diastolic pressure
$Ao_{d\,min}$ = minimal aorti diastolic pressure
Ao_{md} = aortic mean diastoli pressure
mAo = mean ortic pressure
PA_s = pulmonary artery systolic pressure
PA_d = pulmonary artery diastolic pressure
CVP = central venous pressure
CO = cardiac output
SV = strok volume
SVR = systemic vascular resistance
LVSW = left entricular stroke work
A HR = product of systolic blood pressure and heart rate

Table 15 Hemodynamis ffects of IABP in case EB Mean of all estimations during the 90 hour period of assistance

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm H	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min	ml	units	gm m/beat	mm Hg beat/min
Pump off	90	81	77	62	69	70	26	16	14	1.8	20	31	23	8100
Pump on	76	66	98	45	80	74	25	15	13	2.0	22	31	21	6800
Difference	—14	—15	+21	—17	+11	+4	—1	—1	—1	+0..	+	0	—2	—1300
Difference in per cent of pump off value	—16	—19	+27	—27	+16	+6	—4	—6	—7	+11	+10	0	—9	—16
P	<0 001	<0 001	<0.001	<0.001	<0 001	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S	<0 001

Abbreviations see T ble 14.

Table 16 Hemodynamic effects of IABP in case SR. Mean of all estimations during the 41 hour period f assistance

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm H	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min.	ml	units	gm m/beat	mm Hg beat/min
Pump off	7	5	50	43	46	48	40	27	9	2.5	23	16	8	5900
Pump on	51	46	77	38	55	53	39	26	9	6	24	17	7	5300
D fference	—6	—6	+22	—5	+9	+5	—1	—1	0	+0.1	+1	—1	—1	—600
D fference in per cen f pump ff alue	—1	—1	+44	—1	+20	+10	—3	—4	0	+4	+4	—6	—13	—10
P	N S	05	001	<0 05	<0 001	N.S	N.S	N.S.	N.S.	N.S.	N.S.	N.S	N.S.	N.S.

Abbreviations see Table 14

Table 17. Hemodynamic effects of IABP in case AA. Mean of all estimations during the 17 hour period of existence

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	L/min	ml	units	gm m/beat	mm Hg beat/min
Pump off	72	65	64	51	56	56	20	14	7	3.6	3	13	15	8000
Pump on	66	57	88	39	68	6	20	14	7	4	37	13	16	7300
Difference	−6	−8	+24	−12	+1	+6	0	0	0	+0.6	+5	0	+1	−700
Difference in per cent of pump off value	−8	−12	+38	−24	+21	+11	0	0	0	+17	+16	0	+7	−9
P	N.S.	N.S.	<0.01	<0.01	<0.05	N.S.	N.S.	N.S.	N.S.	<0.05	<0.05	N.S.	N.S.	N.S.

Abbreviations see Table 14.
= one estimation only

Table 18. Hemodynamic effects of IABP in case EH. Mean of all estimations during the 80 hour period of existence

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	L/min	ml	units	gm m/beat	mm Hg beat/min
Pump off	85	79	77	67	71	75	42	31	7	3.8	35	17	21	9100
Pump on	78	71	94	59	77	76	41	28	7	4.3	42	16	24	8200
Difference	−7	−8	+17	−8	+6	+1	−1	−3	0	+0.5	+7	−1	+3	−900
Difference in per cent of pump off value	−8	−10	+22	−12	+8	+1	−2	−10	0	+13	+20	−6	+14	−10
P	<0.01	<0.001	<0.001	<0.001	<0.01	N.S.	N.S.	<0.05	N.S.	<0.05	<0.01	N.S.	N.S.	<0.05

Abbreviations, see Table 14

Table 19. Hemodynamic effect of IABP. Mean of all estimations in all 5 patients during 17 to 90 hours of isolated circulation

	Ao_s	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA_s	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	L/min	ml	units	gm m/beat	mm Hg beat/min
Pump off	83	75	71	59	64	67	35	23	11	3.0	29	21	21	8300
Pump on	72	64	91	48	74	71	34	21	11	3.3	33	21	21	7200
Difference	−11	−11	+20	−11	+10	+4	−1	−2	0	+0.3	+4	0	0	−1100
Difference in per cent of pump off value	−13	−15	+28	−19	+16	+6	−3	−9	0	+10	+14	0	0	−13
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	N.S.	N.S.	N.S.	N.S.	<0.05	N.S.	N.S.	<0.001

Abbreviations see Table 14

Table 14 Hemodynamic effects of IABP in case AM Mean of all estimations during the 68 hour period of assistance.

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min	ml	units	gm m/beat	mm Hg beat/min
Pump off	91	79	71	57	64	66	29	13	13	3.6	36	16	37	9100
Pump on	76	65	91	46	75	71	29	13	13	3.9	40	16	32	7500
Difference	—15	—14	+20	—11	+11	+5	0	0	0	+0.3	+4	0	—5	—1600
Difference in per cent of pump off value	—16	—18	+28	—19	+17	+8	0	0	0	+8	+11	0	—14	—18
P	<0.001	<0.001	<0.001	<0.001	<0.001	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	<0.001

Abbreviations.

Ao_s	= aortic systolic pressure	PA_d	= pulmonary artery diastolic pressure
Ao_{ms}	= aortic mean systolic pressure	CVP	= central venous pressure
$Ao_{d\,max}$	= maximal aortic diastolic pressure	CO	= cardiac output
$Ao_{d\,min}$	= minimal aortic diastolic pressure	SV	= stroke volume
Ao_{md}	= aortic mean diastolic pressure	SVR	= systemic vascular resistance
mAo	= mean aortic pressure	LVSW	= left ventricular stroke work
PA_s	= pulmonary artery systolic pressure	Ao HR	= product of systolic blood pressure and heart rate

Table 15 Hemodynamic effects of IABP in case EB Mean of all estimations during the 90 hour period of assistance

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min.	ml	units	gm m/beat	mm Hg beat/min.
Pump off	90	81	77	62	69	70	26	16	14	1.8	20	31	23	8100
Pump on	76	66	98	45	80	74	25	15	13	2.0	22	31	21	6800
Difference	—14	—15	+21	—17	+11	+4	—1	—1	—1	+0.2	+2	0	—2	—1300
Difference in per cent of pump off value	—16	—19	+27	—27	+16	+6	—4	—6	—7	+11	+10	0	—9	—16
P	<0.001	<0.001	<0.001	<0.001	<0.001	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	<0.001

Abbreviations see Table 14

Table 16 Hemodynamic effect of IABP in case SR. Mean of all estimations during the 41 hour period of assistance

	Ao	Ao_{ms}	$Ao_{d\,max}$	$Ao_{d\,min}$	Ao_{md}	mAo	PA	PA_d	CVP	CO	SV	SVR	LVSW	Ao HR
	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	l/min.	ml	units	gm m/beat	mm Hg beat/min
Pump off	57	52	50	43	46	48	40	27	9	2.5	23	16	8	5900
Pump on	51	46	72	38	55	53	39	26	9	2.6	24	17	7	5300
Difference	—6	—6	+22	—5	+9	+5	—1	—1	0	+0.1	+1	—1	—1	—600
Difference per cent of pump off value	—11	—1	+44	—12	+20	+10	—3	—4	0	+4	+4	—6	—13	—10
P	N.S.	0.05	<0.001	<0.05	<0.001	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Abbreviations see Table 14

Hemodynamic course during counterpulsation

The individual hemodynamic course during counterpulsation is shown in Table 20 to 24

Comparison of pump off values obtained after start, half a day one day and two days of IABP

The results are shown in Table 25 to 27 and Fig. 13 to 15 Pump off cardiac outputs and pressure recordings after equal periods of IABP were first obtained in all patients at the interval 6 to 8 hours. The findings after half a day one day and two days were then studied. Aortic systolic and diastolic as well as mean systolic and mean diastolic pressures, mean aortic pressure, central venous pressure, cardiac output, stroke volume, left ventricular stroke work and the Aos HR – product successively rose. Pulmonary artery pressures and systemic vascular re sistance were unchanged or declined.

Table 20 Case AM The hemodynamic course during and after IABP

Time from start/ termination of IABP hrs	Ao s/d mm Hg		PA_d mm Hg		CO l/min		SVR units		LVSW gm m/beat		Ao HR mm Hg beat/min	
	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on
	59/47	53/42	10	11	2.1	[illegible]6	19	16	12	11	6500	5800
6	66/50	57/43	14	14	2.0	[illegible]7	[illegible]3	15	11	13	7300	6300
12	77/53	58/41	10	9	6	[illegible]5	18	21	21	14	7700	5800
20	113/67	83/52	11	10	4 1	4 6	15	14	46	36	11900	8700
30	113/68	111/58	14	14	5.2	5 3	13	14	61	56	12000	11800
38	100/57	81/53	15	15	4 0	3 9	14	16	36	30	10300	8300
42	94/56	72/46	15	14	5.0	4.5	11	13	46	31	9600	7300
50	99/58	83/43	12	13	3.9	4.9	15	13	47	46	8900	7500
58	106/65	91/50	11	10	3.6	4.[illegible]	18	15	37	38	10600	9100
62	INTRA-AORTIC BALLOON COUNTERPULSATION TERMINATED											
7	135/77		17		4 4		20		62		13200	
20	110/60		14		4.3		21		82		10000	
29	136/80		18		5.1		17		80		1[illegible]400	

Abbreviations see T ble 14

Table 21 Case EB The hemodynamic course during and after IABP

Time from start/ termination of IABP hrs	Ao s/d mm Hg		PA_d mm Hg		CO l/min		SVR units		LVSW gm m/beat		Ao HR mm Hg beat/min	
	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on	Pump off	Pump on
2	54/41	44/27			1.0	1.1	33	30			4900	4000
6	67/50	56/34			1.6	1.8	25	[illegible]4			6000	5000
14	77/54	64/38			1 7	2.0	[illegible]5	25			6900	5800
20	83/57	68/41			1 7	1 7	29	31			7500	6100
28	105/69	75/44			1 7	1.3	38	48			9500	6800
32	99/66	82/47			1 7	2 0	34				8900	7400
44	96, 67	81/48			1 6	1 7	39	40			8600	7300
48	92/62	92/52			1 7	[illegible]	34	3			8300	8300
54	93/63	85/47			1.8	1.9	34	37			8400	7700
6[illegible]	99/70	84/50	13	13	2 1	2 5	3	[illegible]7	24	22	8900	7600
68	97/66	83/49	16	14	3	2.3	28	29	4	21	8700	7500
7[illegible]	106/71	91/53	11	17	2.1	[illegible]5	3[illegible]	29	26	4	9500	8200
76	101 66	87/52	19	18	2 1	2.5	31	29	22	20	9100	7800
86	88/60	70/40	15	14	0	2.3	[illegible]8	25	19	17	7900	6300
90	INTRA-AORTIC BALLOON COUNTERPULSATION TERMINATED											
7	100/6[illegible]		15		[illegible]5		23		29		8000	
[illegible]2	1[illegible]/70		14		1 8		43		33		8800	

Abbreviations see T ble 14

Tabl 27 Mea of pump off values of th 3 cases (case AM EB and EH) still alive at a ecording 6—8 and at 44—50 hou s after start of IABP

	Ao_s mm Hg	Ao_{ms} mm Hg	Ao_d mm Hg	Ao_{md} mm Hg	mAo mm Hg	PA_s mm Hg	PA_d mm Hg	CVP mm Hg	CO l/min.	SV ml	SVR units	LVSW gm m/beat	Ao_s HR mm Hg beat/min.
6— 8 hrs	75	69	56	61	63	35	6	10	⌐3	24	4	16	7367
44—50 hrs	97	86	67	73	78	33	23	12	3.3	33	22	36	10800
Difference	+22	+17	+11	+12	+15	—2	—3	+2	+1.0	+9	—2	+20	+3433
Difference in per cent	+29	+25	+20	+20	+⌐4	—6	—12	+20	+43	+38	—8	+125	+47

Abbreviation. see Table 14.

Tabl 28 Mean of hemodynamic findings in the two IABP survivors (case AM and EB) at start of and ⌐2 and 29 hours after termination of IABP

	Ao_s mm Hg	Ao_{ms} mm Hg	Ao_d mm Hg	Ao_{md} mm Hg	mAo mm Hg	PA_s mm Hg	PA_d mm Hg	CVP mm Hg	CO l/min.	SV ml	SVR nits	LVSW gm m/beat	Ao_s HR mm Hg beat/min.
At start of IABP	57	5?	44	46	47	—	—	11	1.6	14	26	—	5700
22 and ?9 hrs after termination of IABP	129	115	75	89	95	30	14	13	3.5	41	30	57	10600
Difference	+72	+63	+31	+43	+48	—	—	+2	+1.9	+27	+4	—	+4900
Difference in per cent	+126	+121	+70	+93	+102	—	—	+18	+119	+193	+15	—	+86

Abbreviations see Table 14

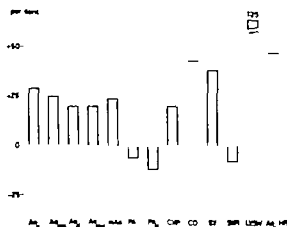


Fig 15 Mean f pump ff alues of the 3 patients (case AM EB and EH ll alive at 6—8 and at 44—50 hours after art f IABP D fference in per cent Abbreviations se Tabl 14

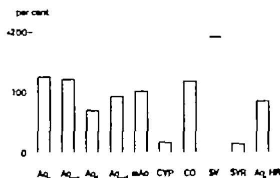


Fig 16 Mean of the hemodynamic findings in the two IABP survivors (case AM and EB) at start of and at 22 and 29 hours fter termination f IABP Difference in per ent Abbreviations see Tabl 14

Post-assist hemodynamics

IABP was terminated in two patients and these were hemodynamically followed for another 22 and 29 hours afterwards. Aortic pressures continued to rise as was the case with left ventricular stroke work.

Table 28 and Fig. 16 shows the mean of the hemodynamics for these two patients at start of IABP and 2_ and 29 hours after termination of circulatory assist.

COMMENTS

Treatment of cardiogenic shock by means of mechanical circulatory assistance has during the last decade been performed with many different methods, both experimentally and clinically. Advantages and drawbacks of these methods have recently been summarized in literature surveys by Soroff et al. (1969), Corday et al. (1970) and Sanders et al. (1971). The counterpulsation method has recently been reviewed by Kuhn (1971) and Corday et al. (1970). The aim of the method is threefold. 1) to augment diastolic pressure of the aorta, thereby increasing the coronary perfusion pressure and the myocardial nutrition, 2) to reduce the aortic end-diastolic and systolic pressure, thereby decreasing the afterload and oxygen consumption of the heart and 3) to increase the perfusion of the peripheral tissues.

Experimentally varying results have been obtained with the intra-aortic balloon counterpulsation technique. A comparison between different reports has been made by Corday et al. (1970), who point out that the differing opinions may be due to variations in the sites as well as techniques of measurement. In several reports (Brown et al. 1968 Talpins et al. 1968 Yahr et al. 1968, Corday et al 1970 Matloff et al. 1970 and Urschel et al 1970) there was a decline of left ventricular peak systolic pressure ranging from 3 to 27 per cent. Matloff et al. (1970) reported an increase (8 per cent) of left ventricular end diastolic pressure but Corday et al. (1970) did not find any significant change (+0.3 per cent). Cardiac output rose 3 to 60 per cent (Yahr et al. 1968, Corday et al. 1970 and Urschel et al. 1970), while two studies (Talpins et al. 1968 and Matloff et al. 1970) reported a reduction by 8 and 10 per cent respectively. Coronary flow increased by 13 to 50 per cent (Talpins et al. 1968, Yahr et al. 1968 and Corday et al. 1970) whereas a decrease by 1 to 5 per cent was found by Brown et al. (1968). Renal flow was reported to decrease by 2 to 27 per cent in two investigations (Talpins et al. 1968 and Corday et al. 1970) and was unchanged in a third one (Brown et al. 1968). Corday et al. (1970) found a reduction in aortic end diastolic pressure (25 per cent), tension-time index (12 per cent) while the peak aortic diastolic pressure increased (35 per cent). Others have also reported a decrease of tension-time index during IABP indicating a diminished myocardial oxygen consumption (Talpins et al. 1968, Yahr et al. 1968 and Braunwald et al. 1969).

Spotnitz et al. (1969) showed that counterpulsation produced reductions of 19 to 25 per cent in peak left ventricular wall stress, increased coronary blood flow by 29 per cent and decreased myocardial oxygen consumption by 10 per cent. Urschel et al. (1970) pointed to the importance of adequate reduction of systolic impedance leading to increased peak aortic flow stroke volume and cardiac output.

Powell et al. (1970) showed that IABP decreased left ventricular peak systolic pressure and left ventricular end diastolic pressure and increased coronary blood flow.

Reduced experimental infarct size after aortic counterpulsation has been reported. Sugg and colleagues (1969) found that counterpulsation used for a period of two hours immediately following circumflex ligation reduced the infarct size to 15 per cent of the total ventricular mass, as contrasted to 28 per cent in control animals. If the use of counterpulsation was delayed _4 hours after coronary ligation, the benefit was diminished. Similar results were obtained by Nachlas and Siedband (1967). Maroko et al. (1971), by use of epicardial electrodes, showed that the surrounding ischemic zone in experimental infarct was increased after

treatment with isoproterenol, bretylium and digitalis and diminished after counterpulsation.

Increased collateral coronary circulation has been reported (Brown et al. 1967, Rosenzweig 1967 and Elliot et al. 1968) whereas others could *find* no such effect (Selmonosky et al. 1971).

There are few clinical series with detailed hemodynamic evaluation of IABP. Bregman et al. (1971) reported on 5 patients with shock due to AMI treated with dual-chambered intra-aortic balloon assist. With the onset of intra-aortic balloon pumping, the systolic blood pressure fell with an average of 11 mm Hg (range 9 to 15 mm Hg), while the peak diastolic pressure after one min. of assist rose by an average of 54 mm Hg (range 42 to 65 mm Hg). The central venous pressure fell on average 8 cm H_2O within the first 30 min. of assists (range 4 to 10 cm H_2O). The duration of assists was 4 to 16, mean 12 hours. Comparing the hemodynamic data immediately prior to assist and after assist was terminated, there was an increase in cardiac index, stroke volume index, stroke work and mean ejection rate, whereas total peripheral resistance declined in all patients.

Mueller et al. (1971) evaluated the effect of *intra aortic counterpulsation with a single chamber* balloon during 22 to 94 hours in 10 patients with shock after AMI. The aortic systolic pressure and left ventricular outflow resistance decreased by 18 per cent during 4 to 6 hours of IABP. An increase in coronary blood flow from on average 68 to 91 ml per 100 g per min. was significantly correlated to a rise in mean arterial pressure. Although the shock state was reversed in all patients, only one of these 10 patients left the hospital. The authors pointed out the desire of early intervention. This was also emphasized in a recent report by Mueller and associates (1972) where the effect of isoproterenol, l-norepinephrine and IABP on hemodynamics and myocardial metabolism was compared in shock due to AMI. Isoproterenol improved cardiac performance but myocardial oxygenation deteriorated. L-norepinephrine improved myocardial perfusion and oxygenation while cardiac output remained unchanged.

Coronary blood flow, myocardial oxygen consumption and hemodynamics were measured on and off IABP 14 times in 10 patients with shock secondary to AMI (Leinbach et al. 1971). At the time of study an average of 14 hours of IABP had elapsed. Coronary blood flow fell in 7 instances, was unaffected in 3 and rose in 4. Changes in myocardial oxygen consumption correlated closely with the observed effects on coronary blood flow. Systolic arterial pressure fell by an average of 11 mm Hg with IABP while mean diastolic pressure rose 8 mm Hg.

Dunkman et al. (1971) recently reported on 39 patients with shock due to AMI treated with IABP by use of a three-segmented balloon. After 24 to 48 hours the cardiac index had increased by 700 ml per min. and square meter. The mean arterial pressure had increased 8 mm Hg and the pulmonary wedge pressure had decreased 4 mm Hg.

Summers et al. (1969) studied 3 patients in shock due to *AMI treated with IABP. The mean* systolic pressure was reduced by an average of *8 per cent and mean diastolic pressure increased* by an average of 21 per cent during the pumping period. The left ventricular end diastolic pressure was reduced by an average of 50 per cent.

These clinical reports have found, low cardiac outputs prior to assisted circulation, progressively rising during the pump period. Also other hemodynamic parameters moved towards normal. The same was observed in the present study indicating *that cardiac performance improved during the* counterpulsation. The aortic systolic pressure times heart rate product decreased significantly during counterpulsation in the present series, suggesting a diminished myocardial oxygen demand.

SUMMARY

A monosegmented intra-aortic balloon catheter could be adequately positioned in the aorta *in* all 6 patients submitted for IABP in spite of co-existing sclerosis of the femoral artery and no complication occurred from this procedure. Five of

these patients were treated with IABP and shock was reversed in all. Two patients left the CCU and one is still alive one year later The causes of death were extensive infarcts in three patients and rupture with cardiac tamponade in one.

IABP decreased the aortic peak systolic pressure (mean 13 per cent) and increased the mean diastolic pressure (mean 16 per cent) significantly The cardiac output did not change significantly The product of the aortic systolic pressure and the heart rate, used as an indirect measure of myocardial oxygen demand, decreased by 13 per cent.

Measurements while the pump was off showed that the aortic systolic and diastolic pressures progressively rose during the first days of IABP The cardiac output and the left ventricular stroke work likewise increased.

PART V

Prediction of shock)*

The mortality of shock associated with AMI is still very high in all age groups (Killip and Kimball 1967 Kuhn 1967 Lawrie et al. 1967 Lown et al. 1967 b, Wallace et al. 1967 Scheidt et al. 1970, Swan et al. 1970 and Wan et al. 1971). Despite treatment in CCUs with different methods the mortality is 59 to 100 per cent. How ever it is possible that these poor results may improve if therapeutic methods were instituted at an earlier stage, consistent with the probable benefit of prophylactic and early treatment of premalignant arrhythmias. In order to test this hypothesis a simple and rapidly performed index is first needed that immediately on admission to CCU or at least before the patient is hypotensive, could predict shock. Shock therapy such as volume loading, different drugs and assisted cir culation could then be instituted prophylactically provided the complications of these methods are low or the discrimination ability of the index is high.

Much has been published about the prognosis in AMI (Schnur 1953 Peel et al. 1962, Hughes et al. 1963 Lemlich 1965 Norris et al. 1969a and 1969b, Bullock et al. 1970, Hughes et al. 1971 and Selvini et al. 1971) and some reports have resulted in a prognostic index (Peel et al. 196_, Hughes et al. 1963 Norris et al. 1969a, Bullock et al. 1970 and Selvini et al. 1971) These indices, however concern the mortality risk only and they give n[illegible] ndication of the mode of death. W th the [illegible] of prophylactic treatment it is more essential to know how the patient will die rather than that he [illegible] high risk to die.

The severity of [illegible] been graded by different methods in [illegible] the prognosis (Broder and Weil 1964 Noble 1969 Shubin et al. 1968, Scheidt and Fillmore 1970 Scheidt et al 1970 and Swan et al. 1970) and an index for quantification of severity and prognosis of shock complicating myocardial infarction has been presented (Shubin et al. 1968 and Shubin 1969). In all these studies however shock was already fully established.

Recently Thompson and Sloman (1971) found that a past history of congestive heart failure, diabetes or hypertension was more important than angina or previous infarction in predicting car diogenic shock. They stressed "the necessity for a systematic approach to predicting complications, and the use of computing techniques in such a study A simple and quick index should preferably be based on a few objective clinical parameters on admission and to my knowledge no such index has been published.

In the present series of 7 patients treated with volume loading or IABP shock could be reversed in all. Yet, all but one died. The main causes of death, extensive infarcts, rupture with cardiac tamponade and shock lung are to-day untrea table, and the only approach to the problem seems to be prophylactic shock treatment before shock or even hypotension has appeared.

All this prompted a search for such a shock predictive index by a retrospective study on a large CCU material.

A. RETROSPECTIVE STUDY

MATERIAL AND METHODS

During January 1 1968 to January 1 1971 there were 55 patients with shock described in Part I

*) First presented at the [illegible] Congress of Cardiology October 1 1971 [illegible] Finland

(page 1?). 33 of these were not in shock on admission but developed it later on *during* the CCU stay. Only these can be taken into consideration when constructing a shock *predict* index. A control group of 272 patients admitted to CCU on the same criteria (page 8) during the same three year period was randomly selected.

To be able to act prophylactically against shock in AMI it is not only necessary to predict shock but also to diagnose AMI. Therefore, the ECG positive individuals of each group, i.e. those with signs suggestive of an AMI on the admission ECG were compared with regard to history as well as the physical and ECG findings on admission. The 23 ECG positive individuals of the 33 shock-developing patients will be referred to as the shock-developing group and the 58 ECG positive individuals of the 272 controls will be called the control group.

Of all clinical data present on admission, 4 numerical parameters were found to differ significantly between the shock-developing and the control group, and discriminant analysis was performed for all combinations of these 4 parameters (heart rate, systolic and diastolic blood pressure and respiratory rate). The program used computes a linear function of a number of variables measured on each individual. This function can serve as an index for discrimination between 2 groups. The statistical theory and method has been described by Anderson and Bancroft (1955) and Kendall and Stuart (1966). Discriminant analysis with this method has previously been applied to medical data in association with AMI (Hughes et al. 1963, Lemlich 1965, Pipberger et al. 1968 and Shubin et al. 1968). The discrimination ability is expressed by a F value. The higher this F value is the better is the discrimination between the two groups.

Sensitivity i.e. the ability of a test to recognize the true positives and specificity i.e. the ability to find the true negatives were calculated according to the following formulae (Cochrane and Holland 1971).

$$\text{Specificity} = \frac{a}{a + c} \times 100$$

$$\text{Sensitivity} = \frac{d}{b + d} \times 100$$

a. individuals who developed shock detected by the test (true positives)

b. non-shock individuals positive to the test (false positives)

c. individuals who developed shock not detected by the test (false negatives)

d. non-shock individuals negative to the test (true negatives)

Discriminant analysis was first performed on the whole groups and to test that the material was not to small the procedure was thereafter repeated for 48 per cent (11 patients) of the shock developing group as well as of the control group (28 patients), randomly selected. Sensitivity and specificity were calculated.

The computed shock index was then tested prospectively in the CCU during 1971.

RESULTS

There were 23 patients in the shock-developing group and 58 in the control group. Thirteen were men and 10 women in the group developing shock and in the control group 39 and 19 respectively. The mean age in the shock-developing group was 68 years and in the control group 65 years ($P > 0.05$). The anamnestic data are shown in Table 29. Previous myocardial infarction was significantly more common in the shock-developing group ($P < 0.05$). No other significant differences were found as regards previous history.

The physical and ECG findings on admission are given in Table 30. There were significantly more patients with bundle branch block in the shock-developing group. No other significant differences were found.

Numerical clinical data available on admission are shown in Table 31 and Fig. 17. Highly statistically significant differences were obtained for heart rate, systolic and diastolic blood pressure and respiratory rate. These 4 parameters only were

used in all possible combinations for discriminant analysis and the specificity at different levels of sensitivity was calculated according to the described formulae. The results as well as the obtained F values are shown in Table 32. The highest F values were obtained for the combination of systolic blood pressure and heart rate (F = 30.5) and of systolic blood pressure and respiratory rate (F = 30.6). In Table 33 it is shown that there was a co-variation between heart rate and systolic blood pressure but not between respiratory rate and systolic blood pressure. Therefore the combination of systolic blood pressure and respiratory rate was chosen. As can be seen in Fig. 18 and 19 no higher specificity at the highest degrees of sensitivity could be gained when the combination of 3 or 4 parameters were used instead of these 2. Adding diastolic blood pressure or the combination of diastolic blood pressure and heart rate to the combination of systolic blood pressure and respiratory rate did not result in higher discriminating power. The calculated discriminant function coefficients were —0.000789 for systolic blood pressure and +0.00282 for respiratory rate.

The score (shock predictive index) for each patient was obtained by the following formula.

$$SPI = 0.00282 \; RR - 0.000789 \; SBP$$

where SPI = shock predictive index

SBP = systolic blood pressure

RR = respiratory rate.

Fortyeight per cent (11 patients) of the shock developing as well as of the control group (29 patients) were randomly selected and discriminant analysis performed for the combinations of the 4 numerical variables. Specificity at different levels of sensitivity was calculated. The highest F values were still obtained for the combinations of heart rate and systolic blood pressure (F = 10.7) and respiratory rate and systolic blood pressure (F = 10.6). Specificity at different levels of sensitivity was calculated for the combination of systolic blood pressure and respiratory rate and is graphically illustrated in Fig. 20 where also the curve of the whole ECG positive group is illustrated. As can be seen the curves follow each other closely

From the formula

$$SPI = 0.0028? \; RR - 0.000789 \; SBP$$

the following equation could be derived.

$$RR = \frac{0.000789}{0.00282} \; SBP + \frac{SPI}{0.00282}$$

This equation is presented as a nomogram in Fig. 21. The patients have also been plotted in this nomogram where only one line is drawn, the 70 per cent sensitivity/97 per cent specificity line, i.e. a SPI above —0.025. The 70 per cent line was chosen because the specificity starts to fall off at this point (Table 32 and Fig. 18). At this level 16 (70 per cent) of the 23 ECG positive individuals could be predicted to develop shock by 1 to 41 hours prior to onset of shock with a mean of 10 hours (Fig. 22). The index failed to predict shock in 7 patients who developed shock

Tabl 29. Anamnestic data in the shock-developing group (23 patients) and the control group (58 patients).

	Shock developing group (n = 23) per cent	Control group (n = 58) per cent	P
Past history			
No previous angina pectoris	39	45	N.S
Angina 1 week to 1 month prior to admission	9	17	N.S.
Angina more than 1 month prior to admission	52	38	N.S.
Previous myocardial infarction	48	19	< 0.05
Heart failure	39	17	N.S.
Hypertension	35	28	N.S.
Valvular disease	4	1	N.S.
Diabetes	9	6	N.S.
Heredity for coronary disease and or diabetes	17	16	N.S.
Symptoms prior to admission			
No central chest pain[1])	9	5	N.S.
Central chest pain without radiation)	13	14	N.S.
Central chest pain with radiation)	78	81	N.S.
Dyspnoea	52	28	N.S.
Fainting or unconsciousness	26	12	N.S.
Arrhythmic sensation	26	12	N.S.
Vomiting or sweating	91	76	N.S.
Physical or psychical effort before onset of symptoms	13	29	N.S.

[1]) Central chest pain for more than 30 min. within the last 48 hours prior to admission.

after 1 to 46 hours, mean 14 hours. The only 2 patients who survived belonged to this group The index also failed to predict shock in another 10 patients because their admission ECG were negative.

Tabl 30 Physical and ECG findings in the shock developing group (23 patients) and control group (58 patients) on admission to the CCU

	Shock developing group (n = 23) per cent	Control group (n = 58) per cent	P
Unconsciousness	0	0	N.S.
Left heart failure	61	38	N.S.
Right heart failure	13	3	N.S.
Sinus rhythm	78	86	N.S.
Atrial fibrillation	17	5	N.S.
Bundle branch block, including hemiblocks	30	2	< 0 001

PROSPECTIVE STUDY

MATERIAL AND METHODS

The shock predictive index was calculated on admission for all 574 patients admitted to the CCU during 1971 177 were later on proven to

Table 31 N merical clinical data in the shock-developing group (23 patients) and control group (58 patients) on admission to the CCU

	Shock developing group n = 23 mean S.D	Control group n = 58 mean S.D.	P
Age, years	68 ± 11	65 ± 10	N.S.
Time from onset of symptoms to CCU-admission, hrs	7 ± 8	9 ± 9	N.S.
Heart rate, beats/min.	108 ± 22	81 ± 20	< 0.001
Systolic blood pressure, mm Hg	116 ± 27	151 ± 23	< 0.001
Diastolic blood pressure, mm Hg	79 ± 15	93 ± 14	< 0 001
Respiratory rate, per min.	28 ± 6	21 ± 5	< 0 001

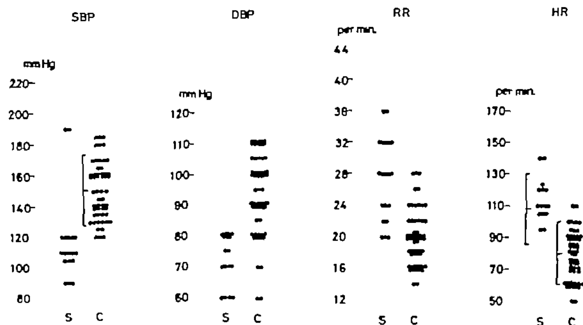


Fig 17 Plot of systolic (SBP) and diastolic (DBP) blood pressure respiratory rate (RR) and heart rate (HR) S = shock-developing group and C = control group Mean and S.D indicated by E.

T ble 32 Specificity (pe cent) at different levels of sensitivity for all possibl combinations of heart ate (HR), systolic (SBP) and diastolic (DBP) blood pressure and respiratory rat (RR)

	Sensitivity per cent										F	P
	9	22	30	39	52	61	70	78	91	100		
HR, SBP	98	98	98	98	98	98	98	91	77	36	30.5	< 0 01
HR, DBP	98	98	98	98	97	93	91	91	62	31	22.8	< 0 01
HR, RR	98	98	98	97	97	88	86	86	76	38	19 0	< 0.01
SBP DBP	100	100	98	98	98	97	95	95	71	5	17.6	< 0 01
SBP RR	98	98	98	98	98	98	97	95	95	[illegible]8	30 6	< 0 01
DBP RR	98	98	98	97	95	93	88	84	83	[illegible]2	17.9	< 0.01
HR, SBP DBP	98	98	98	98	98	98	98	81	69	41	20 1	< 0.01
HR, SBP RR	98	98	98	98	98	98	98	97	81	57	24.5	< 0.01
HR, DBP RR	98	98	98	98	97	97	93	88	84	55	17 1	< 0 01
SBP DBP RR	98	98	98	98	98	98	98	97	95	28	21 1	< 0 01
HR, SBP DBP RR	98	98	98	98	98	98	98	98	83	53	18.5	< 0 01

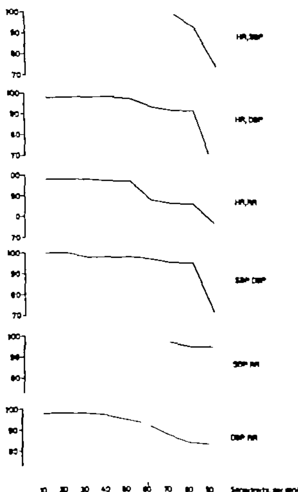


Fig 18 Specificity as function f sensi ity when combining 2 parameters (HR = heart rat SBP = systolic blood pressure, DBP diastolic blood pressure and RR = respirator at)

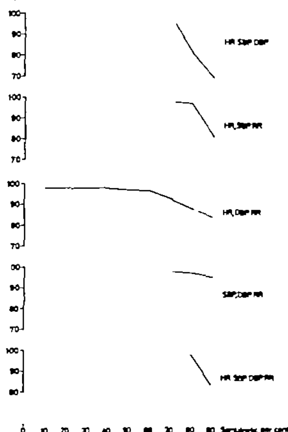


Fig 19 Specificity as f nction f se siti ity when combining 3 and 4 n merical items in all possibl combinations (HR = heart rate SBP = systolic blood pressure DBP = diastolic blood pressure and RR = espiratory rate)

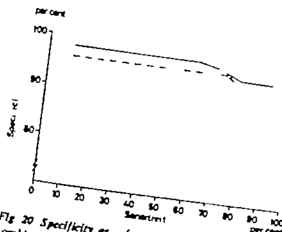
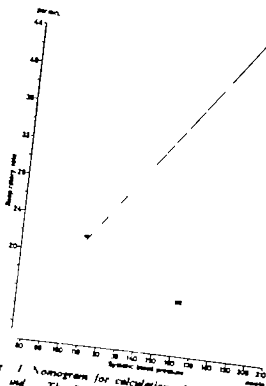


Fig 20 Specificity as function of sensitivity for the combination of systolic blood pressur and respiratory rate

——— *= all patients*

- - - *= 48 per cent of the patients*



F g / Nomogram for calculation of shock predic n and Th 70 per cnt sensiti ity-97 per cent pecific l ne is drawn. The 23 shock-devel ping patie (o and the 58 control ( ) ar plotted

T ble 33 Correlation matrix (HR=heart rate SBP=systolic blood pressur DBP=diastolic blood pressure RR= expiratory rate)

	HR	SBP	DBP	RR
HR	1 0	−0.28	−0.22	0 49*
SBP		1 0	0.83	−0 02
DBP			1.0	−0.29*
RR				1 0

significant, P < 0 05
significant, P < 0.01
significant, P < 0.001

have an AMI according to the criteria described on page 10 and 85 of these had signs of AMI on their first ECG Of the 177 patients with AMI altogether 15 patients (9 per cent) had shock. Seven of them were n shock already on admission and the remaining 8 patients developed shock during their CCU stay

RESULTS

All but one (88 per cent) of the 8 shock-developing patients and 75 (46 per cent) of the 162 non-shock patients with AMI had ECG signs suggestive of AMI on their admission ECG This difference is significant (P < 0 05) Three of the 85 patients with a positive ECG on admission were in shock when first seen. The remaining 82 admission ECG positive individuals have been plotted in the nomogram (F g. 23) When using the 70 per cent sensitivity level from the retrospecti e part, 6 of 7 (86 per cent instead of 70 per cent) shock patients were found by the index. The difference is not significant (P > 0 05) Six of 75 non-shock patients (8 per cent instead of 3 per cent) were falsely predicted. Nor is this difference significant (P > 0.05) The 6 predicted patients developed shock from 1 to 24 mean 8 hours after admission.

COMMENTS

It has been shown that shock in AMI is not necessarily associated with large infarcts (Harnarayan et al. 1970)

Page et al. (1971) found that patients with shock consistantly showed marginal extension of the

SBP	RR	SPI
90	44	0053
100	36	0023
90	32	+0.019
105	36	+0.019
80	28	+0.016
90	28	0008
110	33	+0006
105	30	+0002
120	32	-0004
120	32	-0004
9	24	-0007
120	28	-0016
110	24	-0019
140	32	-0020
110	22	-0025
110	22	-0025
95	20	-0030
105	16	0038
120	20	-0038
120	20	0038
135	24	-0.039
190	28	-0071
190	28	-0071

ADMISSION

20 15 10 5 5 10 15 20 25 30 35 40 45 50 hrs

INDEX POSITIVE

INDEX NEGATIVE

S S

Fig 22 Time from onset f symptoms to admission and t onset of shock, time in shock and utcome in th 23 shock-devel ping patient Systolic blood pres sure (SBP) espiratory rate (RR) and calculated shock predictive index (SPI) on admission are given as is also the 70 per cent sensitivity line separating the index positive and negative individuals. S = survived Dott d line = time in shock.

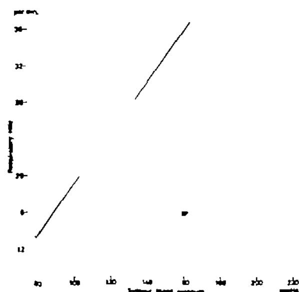


Fig 23 The 7 shock-developing (○) and 75 non shocked (•) patients from the pro pective study are plotted in the shock predictive nomogram Line indicates the 70 per cent sensitivity-97 per cent pecificity level from the retr pective study

recent infarct and scattered areas of necrosis and hemorrhages in the rest of the left ventricular myocardium.

In a recent clinical pathological report of 22 patients with AMI and shock, Scheidt et al. (1972) concluded that established cardiogenic shock was the result of massive myocardial damage, averag ing 50 per cent of the left ventricular mass, that myocardial damage frequently occurred in a stepwise or progressive fashion and that un-

recognized extension of infarction often was the final precipitating factor in the genesis of shock. "The obvious implication is that therapy that minimizes myocardial damage or limits extension of infarction may be able to prevent shock.

These findings encourage as early a treatment as possible, i.e. prophylactic. Early treatment with intra-aortic balloon counterpulsation has been proposed by several authors (Harnarayan et al. 1970, Feola et al. 1971, Kuhn et al. 1971, Mueller et al. 1972). However assisted circulation cannot be claimed to be completely without serious risks. It therefore has to be used restrictively in prophylaxis. At least one case of rupture of an intra-aortic balloon during counterpulsation in man has been reported (Mueller et al. 1971). Other forms of shock therapy carry their risks. Generally prophylactic shock treatment with few and harmless side effects can allow a low specificity of the predictive index, whereas a high specificity is needed with a prophylactic method with risks for frequent and serious complications. Different sensitivity/specificity lines have therefore been calculated and drawn in the nomogram (Fig. 24).

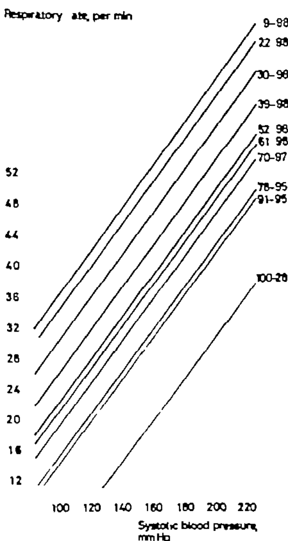


Fig. 24. Nomogram for the shock predictive index (SPI). The lines indicate different levels of sensitivity from 9 to 100 per cent. Sensitivity — specificity is marked on each line. Shock patients will more or less often fall above the lines.

It would be of advantage to have an index that can be calculated rapidly by the CCU nurse and which takes into account only relatively objective parameters. To form the present shock predictive index (SPI), blood pressure, respiratory rate and ECG on admission are used. Regarding these three factors it could be argued that the first obtained blood pressure and respiratory rate may be influenced by pain, anxiety etc. on admission. However as can be seen in Table 34 the difference between the shock-developing group and control group was essentially the same at one and two hours after admission as on admission.

To investigate the variation between the nurses' observations, blood pressure and respiratory rate were measured on admission by two nurses 1 to 20, mean 8 min. apart in 10 patients. The measurements were made independantly of each other. As can be seen from Fig. 25 and 26 there was a close relation between the measurements of systolic blood pressure ($r = 0.97$, $P < 0.001$) and respiratory rate ($r = 0.90$, $P < 0.001$) obtained by the nurses.

If the obligate ECG criterion of the present index is excluded there would be many false positive shock predictions, especially in patients with frank pulmonary oedema because of the high respiratory rate.

Table 34 Systolic blood presser and espiratory ate at 0 1 and 2 hours aft admission t CCU for the shock-developing group and the control group Patients who developed shock within these two hours were subsequently excluded.

	Systolic blood pressure, mm Hg				Respiratory rate, per min			
	Shock developing group mean	Control group mean	t	P	Shock-devlopi g group mean	Control group mean	t	P
On admission	116	151	5 97	< 0 001	28	21	4.94	< 0 001
One hour after admission	109	147	5.69	< 0 001	30	20	6.26	< 0.001
Two hours after admission	109	147	5.94	< 0.001	31	1	5 84	< 0.001

Laboratory tests including blood gas determinations obtained on admission were not taken into consideration in the present evaluation, as the results will not be available until some hour after the admission.

Applying the 70 per cent sensitivity level in the retrospective study there were 7 shock-developing patients who were wrongly predicted as non-shock patients. Two of these survived and the rest died in the CCU There were also two non-shock patients who were falsely predicted to develop shock. None of these died.

In the prospective study one shock-developing patient was wrongly predicted not to develop shock. This patient died during after-care. Six non-shock patients were falsely predicted to develop shock and 2 of these died in CCU

During the prospective study some of the shock predicted patients have been treated prophylactically with shock therapy and others have served as controls. However the series still is too small to be presented.

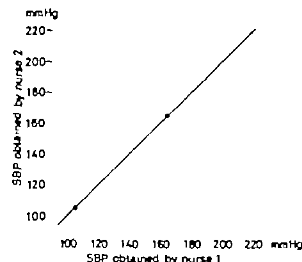
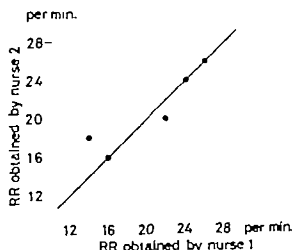


Fig 25 S stolic blood pressure (SBP) btained by two nurses on 10 admissions t th CCU Line indicates identity



F g 26 Respiratory rat (RR) btained by two nurses on 10 admissions to the CCU Line indicates identity

SUMMARY

A shock predictive index has been constructed for patients with ECG signs suggestive of AMI on admission to the CCU. The index is based on systolic blood pressure and respiratory rate on admission. The lower the blood pressure and the higher the respiratory rate, the greater is the risk of developing shock. At the level of 70 per cent sensitivity there was a specificity of 97 per cent.

This index with the above sensitivity level was used prospecti ely during one year and 6 patients predicted on admission to develop shock did so 1 to 24 hours later. There were one false negative and 6 false positive predictions among the 8 patients with ECG signs suggestive of AMI o admission

of AMI on admission to the CCU. The index is based on systolic blood pressure and respiratory rate on admission. The lower the blood pressure and the higher the respiratory rate, the greater is the risk of developing shock. At the level of 70 per cent sensitivity there was a specificity of 97 per cent.

This index with the above sensitivity level was used prospectively during one year and 6 patients predicted on admission to develop shock did so 1 to 24 hours later. There were one false negative and 6 false positive predictions among the 87 patients with ECG signs suggestive of AMI on admission.

References

ADGEY A. A. J ALLEN J D GEDDES, J S JAMES, R. G G WEBB, S. W ZAIDI, S. A. & PANTRIDGE, J F Acute phase of myocardial infarction. *Lancet 2.501 1971*

AGRESS, C. M. & BINDER, M. J Cardiogenic shock. *Amer Heart J 54·458 1957*

AGRESS, C. M., ROSENBURG M., SCHNEIDER MAN, A. & BROTMAN E. J Blood lume studies in shock resulting from myocardial infarction. I. *Studies with evans blue dye (T 1824) J Clin I vest 29 1267 1950*

ALLEN H. N DANZIG R. & SWAN H. J C Incidence and significance f relativ hypovolemia as cause of shock associated with acute myocardial infarction. *Circulation 35—36 suppl 2—50 1967*

ANDERSSON R. L. & BANCROFT T A. Statistical theory in research. *McG aw-Hill 1955*

ARNTZENIUS, A. C., KOOPS, J & HUGEN HOLTZ, P G Cardiovascular responses in piglets to body acceleration given synchronously with the heartbeat (BASH). *Circulation 39—40 suppl 3—38 1969*

BALCON R., HOY J & SOWTON, E Haemodynamic effect of rapid digitalization following acute myocardial infarction. *Brit Heart J 30.373 1968*

BEVEGÅRD S., JONSSON B & KARLÖF L A percutaneous technique for catheterization f the pulmonary artery without fluoroscopy *Brit Heart J 26 842 1966*

BINDER, M. J RYAN, J A., MARCUS, S MUGLER, F STRANGE, D & AGRESS, C M Evaluation f therapy in shock following acute myocardial infarction. *Amer J Med 18 622 1955*

BIÖRCK, G., LUNDMAN T MOGENSEN L & ORINIUS, E Experiences from coronary care unit. *Arch. Klin. Med. 216 242, 1969*

BIÖRCK, G MOGENSEN L NYQUIST O ORINIUS, E. & SJÖGREN A. Studies in myocardial rupture with cardiac tamponade in cute myocardial infarction. I. *Clinical features. Chest 61 4 1972*

BLOOMFIELD D K., SLIVKA, J VOSSLER, S & EDELSTEIN J Survival in acut myocardial infarction before and after the establishment of coronary care unit. *Chest 57 224 1970*

BOUCHARD R. J GAULT J H. & ROSS, J J Comparison of pulmonary arterial end diastolic pressure in patients with and without left ventricular disease. *Circulation 39—40 suppl 3 49 1969*

BRADLEY R. D Diagnostic right-heart catheterization with miniature catheters in severely ill patients. *Lancet 2 941 1964*

BRADLEY R. D JENKINS, B. S. & BRANTHWAITE, M. A. The influence of atrial pressure on cardiac performance f ll wing myocardial infarction complicated by shock. *Circulation 42 827 1970*

BRANTHWAITE, M. A. & BRADLEY R. D Measurement f cardiac output by thermal dilution in man. *J Applied Phys. 24·434 1968*

BRAUNWALD E.. Topics in clinical medicine.*Johns H pkins Med. J 121 6, 421 1967*

BRAUNWALD E., COVELL, J W MAROKO P R. & ROSS, J J Effects f drugs and of counter pulsation on myocardial oxygen consumption. Observations on the ischemic heart. *Circulation 39—40:220 1969*

BREGMAN D GOETZ, R. H & STATE, D Clinical experience with new cardiac assist device. The dual-chambered intra-aortic balloon assist. *J Thorac. Cardiovasc Surg 62.577 1971*

BRODER, G & WEIL, M. H Excess lactate: an index of reversibility of shock in human patients. *Surg 6 127 1968*

BROWN, B. G GOLDFARB D TOPAZ, S R. & GOTT V L. Diastolic ugmentation by intra rtic balloon. circulatory hemodynamics and treatment of severe, acute left ventricular failure in dogs. *J Thorac Cardiovasc Surg 53 789 1967*

BROWN, B G GUNDEL, W D & McGINNIS, G E. Improved intra-aortic balloon diastolic augmentation with double-balloon catheter in the ascending and the descending thoracic aorta. *Ann Thorac Surg 6 127 1968*

BUCKLEY M. J LEINBACH, R. C KASTOR, J A LAIRD J D KANTROWITZ, A R., MADRAS, P N SANDERS, C. A. & AUSTEN W G Hemodynamic evaluation of intra-aortic balloon pumping in man. *Circulation 41—42 suppl 2—130 1970*

BULLOCK, W R., FOSTER, G L RUSSEL, J R O & CASTEN G G. An index to the severity of acute myocardial infarction *Alabama J Med Sci 7 14 1970*

CHATTERJEE, S. & ROSENSWEIG, J Evaluation of intra-aortic balloon counterpulsation. *J Thor Cardiov Surg 61 405 1971*

CHRISTIANSEN L, IVERSEN, K. & SKOUBY A. P Benefits btained by the introduction of coronary-care unit A comparative study *Act med scand 189·285 1971*

CLAUSS, R. H., BIRTWELL, W C., ALBERTAL, G LUNZER, S TAYLOR, W J FOSBERG A. M. & HARKEN D E.. Assisted circulation. I. The arterial counterpulsator *J Thor Cardiov Surg 41·447 1961*

effects f acute myocardial infarction in man. *Progr Cardiovasc. Dis 9.571 1967*

SHUBIN H., AFIFI A. A., RAND W M & WEIL, M H.. Objective index of hemodynamic status for quantitation of severity and prognosis of shock complicating myocardial infarction. *Cardiovasc Res 4.329 1968*

SHUBIN, H.. The development of an index to grade the severity f shock following myocardial infarction. *J Trauma 9 152 1969*

SJÖGREN A Left heart failure in acute myocardial infarction. A clinical, heamodynamic and thera peutic study *Acta Med Scand suppl 510 1970*

SLOMAN G & HUNT D The incidence of left ventricular failure and cardiogenic shock. *Personal communication, 1971*

SMITH, W W WIKLER, N S. & FOX, A. C. Hemodynamic studies of patients with myocardial infarction. *Circulation 9.352, 1954*

SOLOMON H. A., SAN MARCO M A., ELLIS, R. J & LILLEHEI, C. W.. Cardiac output deter mination. superiority of thermal dilution. *Surg For m 20 28 1969*

SOROFF H. S., GIRON F RUIZ, U BIRTWELL, W C. HIRSCH, L J & DETERLING Jr R. A.. Physiologic support of heart ction. *New Eng J Med 280·693 1969*

SPANN J J F BUCCINO R. A., SONNENBLICK, E. H. & BRAUNWALD E. Contractile state of cardiac muscles obtained from cats with experimentally produced ventricular hypertrophy and heart failure. *Circ Res. 11.341 1967*

SPOTNITZ, H. M COVELL, J W ROSS, Jr J & BRAUNWALD E. Left ventricula mechanics and oxygen consumption during arterial counterpulsation. *Amer J Physiol 217 1352 1969*

STANNARD, M SLOMAN G & SANGSTER, L.. Haemodynamic effects of lignocaine in acute myocardial infarction *Brit Med. J 2.468 1968.*

STOCK E., GOBLE A. & SLOMAN G Assessment of arrhythmias in myocardial infarction. *Brit Med J 2 719 1967*

SUGG W L., WEBB W R. & ECKER, R. R. Reduction of xtent of myocardial infarction by counterpulsation. *Ann Thorac Surg 7.310 1969*

SULLIVAN J M & GORLIN R. Effect of 1 epinephrine on the coronary circulation in human subjects with and without coronary artery disease. Circ. *Res. 21·919 1967*

SUMMERS, D N KAPLITT M NORRIS, J RUBIN R., NACHT R ARIEFF A., LEE, M WECHSLER, B & SAWYER, P N Intra-aortic balloon pumping. Hemodynamic and metabolic effects during cardiogenic shock in patients with triple coronary artery obstructiv disease *Arch. Surg 99 733 1969*

SWAN H. J C., FORRESTER, J S., DANZIG R. & ALLEN H. N Power failure in acute myocardial infarction. *Progr Cardiovasc Di 12.568 1970*

TALPINS, N L., KRIPKE, D C. & GOETZ, R. H.. Counterpulsation and intra-aortic balloon pumping in cardiogenic shock. Circulatory dynamics. *Arch Surg 97:991 1968*

THOMAS, M MALMCRONA, R. & SHILLINGFORD J Hemodynamic changes in patients with acute myocardial infarction *Circulation 31 811 1965*

THOMPSON P L. & SLOMAN G Acute myocardial infarction, predictors f arrhythmias and shock. *Ann Clin Res 3.377 1971*

TURNER, A. F MEYERS, H. I JACOBSON G & LO W Carbon dioxide cineangiocardiography in the diagnosis of pericardial disease. *Amer J Roentgen 97.342 1966*

URSCHEL, C. W EBER, L., FORRESTER, J MATLOFF J CARPENTER, R. & SONNENBLICK, E. Alteration f mechanical performance of the ventricle by intra-aortic balloon counterpulsation. *Amer J Cardiol 25 546 1970*

VALENTINE, P A., FLUCK, D C., MOUNSEY J P D REID D., SHILLINGFORD J P & STEINER, R. E. Blood-gas changes after myocardial infarction. *Lancet 2 837 1966*

WALLACE, A. G KLEIN R. F KLINER, V ZIPES, D. & ANDREOLI K.. Coronary care units, their goals, current experience and future *Cardiologia 50·337 1967*

WAN S. H THOMPSON P L., DOWLING J T & SLOMAN G Cardiogenic shock. A review of one yea s experience. *Med J Aust 1 1000 1971*

WEIL, M H. & SHUBIN, H. Shock following acute myocardial infarction. Current understanding of hemodynamic mechanisms. *Progr Cardiovasc Dis 11 1 1968.*

WERKÖ L., LAGERLÖF H., BUCHT H., WEHLE, B & HOLMGREN A.. Comparison of the Fick and Hamilton methods for the determination of cardiac output in man. *Scand J Clin. Lab I est 1 109 1949*

VOGEL, J H. K., KELMINSON L. L. & COTTON E. K. Prolonged observ tion of pulmonary rterial pressure. *Amer Heart J 70·429 1965*

WORLD HEALTH ORGANIZATION Ischemic heart disease registers Report of the fourth work ing group. *Euro 5010 (4) Copenhagen 1970*

YAHR, W Z., BUTNER, A. N KRAKAUER, J S TOMECEK, J TJØNNELAND S. & KANTROWITZ, A.. Cardiogenic shock. dynamics of coronary blood flow with intra-aortic phase shift balloon pumping. *S g Forum 19 142 1968*

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Venous occlusion plethysmography in 55-year old men

A population study in Malmö, Sweden

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MALMÖ GENERAL HOSPITAL, UNIVERSITY OF LUND, SWEDEN

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BY

SVEN-OLOF ISACSSON

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CONTENTS

1 INTRODUCTION

Arteriosclerosis with its complications is a predominant cause of incapacity and death in developed countries. Against this background intensive research on the epidemiology of cardiovascular diseases has been carried out during the last two decades. Many longitudinal studies have been performed, perhaps the best known being the Framingham (Dawber *et al* 1951) and Tecumseh studies (Epstein 1960).

At an early stage, the cardiovascular section of the World Health Organization (WHO) showed an interest in epidemiological investigations of arteriosclerosis as well as of other cardiovascular diseases (WHO Chronicle 1965). Therefore, the cardiovascular diseases have become international concerns and WHO has played an important co-ordinating rôle in the accomplishment of studies in different member states (Keys *et al* 1967).

Arteriosclerosis can be regarded as a systemic disease, but with predilections for three vascular regions. These predilections are for the coronary arteries, the cerebral arteries, and the femoral arteries. Furthermore, the degree of arteriosclerosis may vary considerably from one vascular region to another. This has been clearly shown in the extensive autopsy study by Sternby (1968).

Modern computer technique has made it possible to evaluate many factors and their interrelations which are pertinent to the epidemiological study of arteriosclerotic diseases. Coronary artery disease has thus been subjected to the most intensified study. The factors found to have the strongest correlation to coronary artery disease are smoking, hypercholesterolaemia, hypertension, and lack of physical activity. These factors are generally called *risk factors* which means that a statistical correlation has been demonstrated between these factors and coronary artery disease.

Obesity was also considered an important risk factor in coronary artery disease, but later research suggests that this condition is probably less important than the others previously mentioned (Keys 1970).

Other risk factors have also been found, but they have been either very little studied or proved to have a weaker relation to coronary artery disease. Nonetheless, some of these are worth mentioning and include electrocardiographic abnormalities, personality variables, heredity, diabetes mellitus, hypertriglyceridaemia, lipoprotein electrophoretic abnormalities, high haemoglobin concentration and hyperuricaemia. Thorough reviews of the vast literature in this field were provided by Epstein (1965) and Simborg (1970). Later investigations have shown that high resting heart rate also is an important risk factor (Berkson *et al* 1970).

Even though the interest in earlier epidemiological studies was focused mainly on coronary artery disease, considerable interest has recently been demonstrated in the epidemiology of cerebrovascular diseases (Kuller *et al* 1969, Dawber and Thomas 1969). The Framingham

study (Dawber and Thomas 1969) showed that hypertension hypercholesterolaemia, diabetes mellitus, smoking, obesity and high haemoglobin concentration were risk factors for cerebrovascular disease (stroke). Several of the risk factors consequently are important in both coronary and cerebrovascular disease. However this does not eliminate the possibility that the individual risk factors might be more strongly related to one of these diseases than to the other Several investigations, most notably those by Bjurulf (1964) and Sternby (1968) disclosed a much stronger correlation between hypertension and arteriosclerosis of the cerebral vessels than between hypertension and arteriosclerosis of the coronary vessels.

During the 15 last years, interest in the epidemiology of cardiovascular diseases has increased strikingly in Sweden (Forssman and Lindegård 1958, Nilsson *et al* 1964 Blörck 1965 Tibblin *et al* 1965 Carlson and Lindstedt 1968 Furberg *et al* 1972) and also in many other countries. In Sweden, the cardiovascular diseases represent an important cause of early incapacity and death not only among the aged but also in the middle-aged working population. About one half of all deaths of those in their productive years are caused by these diseases (Werkö 1969). Arteriosclerosis is the foremost of the cardiovascular diseases.

Population studies have been carried out in Gothenburg of both men and women (Tibblin *et al* 1965 Tibblin 1969) and the incidence of myocardial infarction and stroke has been studied with the aid of special infarction (WHO 1969 1970) and stroke (WHO 1971) registers, as recommended by WHO Furthermore, a vast study is in progress, primarily preventive in nature, which will examine the dangers of combination [illegible] factors (Wilhelmsen *et al* 1971)

The res lts of [illegible] res [illegible] study are based on an investig t on car [illegible] ou [illegible] lmo where the interest ir h epide iol [illegible] rdi vascular diseases h been ve g [illegible] more than a decade [illegible] *et al* 19 [illegible] psy t d es of myocardial infarctions in Malmö during the years 1954—1959 have been reported by Söderström (1961). Bjurulf (1964) focused his interest on atherosclerosis in different parts of the arterial system Sternby (1968) studied the frequency of occurrence of atherosclerosis in a defined population Bjurulf *et al* (1967) evaluated cardiovascular symptoms and ECG-findings and related these to carefully performed autopsy examinations with special attention to the coronary arteries and the heart Also a comparison of blood pressure taken under casual and basal conditions as related to the degree of arteriosclerosis was carried out by Bjurulf and Sternby (to be published)

The Malmö studies, referred to above, illustrate the extent of local interest in the epidemiology of cardiovascular diseases and provide a precedent from which to launch further research in this field The present work was designed as a clinical pathological study the first aspect of which was a cross-sectional investigation of randomly selected men Clinical follow up studies were planned and after death every subject was to undergo a special autopsy of the vascular system (cerebral vessels, coronary vessels, aortic parts, and leg arteries from the hip to the ankle with preservation of these blood vessels in formaldehyde sacks). In this situation a comparison would be possible between data collected earlier in connection with the clinical study and the pathologic-anatomical appearence of the arterial system.

Manifestations of disease from two of the three favoured locations for arteriosclerosis (the coronary arteries and the cerebral arteries) have been studied epidemiologically The interest in the third place of predilection (femoral arteries) has been smaller It therefore seems appropriate to cite G Schettler's introductory speech at the Second International Symposium on Atherosclerosis "What are the problems we should deal with in the future? As a clinician I would like to mention a few points. Epidemiology should focus not only on coronary heart disease but also on other vascular areas and

should use all available diagnostic tools. The risk factors in atherogenesis will have different weights in different vascular areas." (Schettler 1970) Technically it is easier to study the circulation in the legs than to study the coronary or the cerebral circulation. In connection with an epidemiological investigation regarding heart diseases, vascular diseases, and lung diseases in 55-year-old men, it was considered important to direct some attention to the peripheral arterial tree as well.

No studies are available in the existing literature which describe attempts at objective measurements of the leg blood flow in a randomly selected material. In the previously mentioned epidemiological investigations, the methods for examining the circulation of the legs has been medical history and pulse palpation. Because of this, intermittent claudication has sometimes become a diagnosis synonymous with arterial obliteration (Fodor *et al* 1968)

However medical history and pulse palpation have proved to be poor methods for surveying the prevalence of femoral stenoses or occlusions in a large population. This has been shown in several reports by Widmer and his co-workers (1963 1967 and 1970). With a special method of investigation including not only medical history but pulse palpation, oscillometry and auscultation before and after leg exercise, Widmer examined a large number of men and women employed by the Swiss pharmaceutical factories in Basel. In this selected material, he was able to verify a preliminary diagnosis of femoral artery disease angiographically in 90 / of the cases detected with the described methods. He observed that stenoses or occlusions in the femoral arteries existed in 1 / of the men aged 40—50 and increased successively by year to about 7 / in men aged 65—74 Higher incidence has been reported in hospital patients (Marti 1961). Widmer also analysed the relation between risk factors in cardiovascular disease and coexisting stenosis and occlusion in the femoral arteries (Widmer *et al* 1969) He was able to demonstrate that systolic hypertension, heavy cigarette smoking, and increased beta-lipoproteins in serum were more common in individuals with occlusions of the arteries of the legs than in individuals without arterial diseases. But there were no differences in cholesterol level or obesity between persons with and without arterial diseases.

It is much easier to measure quantitatively the blood flow in the leg arteries than in other vascular regions, such as coronary arteries or cerebral arteries. In the present study venous occlusion plethysmography was used in order to objectively measure the arterial flow capacity of the legs. The objectives were

(1) to evaluate the utility of venous occlusion plethysmography as a method of epidemiologic investigation

(2) to validate the diagnosis of intermittent claudication established with the aid of a cardiovascular questionnaire (Rose and Blackburn 1968) against the results of venous occlusion plethysmography·

(3) to compare the results of venous occlusion plethysmography with other data gathered in connection with the population study (medical history clinical findings, laboratory data).

The investigation is a cross-sectional study Follow up studies are planned

2. DESCRIPTION OF THE STUDIED POPULATION

Demographic and geographic data

Based on its number of inhabitants, Malmö is the third largest city in Sweden. It is situated on the far south west coast. The climate is relatively mild by Swedish standards, the coldest month being February average temperature −0 7 C. July is the warmest month, average temperature +17.3 C it also has the greatest precipitation (average 65 mm), and March the lowest (30 mm)

The census reported on December 31 1969 revealed that Malmö had 258,311 inhabitants 125 058 men and 133,253 women. The same census showed that the inhabitants of Malmö represented 3.22 / of the total population of Sweden (Statistisk Årsbok, Malmö 1970) There is a relative equilibrium between the number of people moving in and out of the city In 1967 and 1968, respectively approximately 11 000 persons moved into the city and about the same number moved out.

There are three hospitals in Malmö The main hospital, *Malmö General Hospital* is a university hospital and is well represented in the various medical specialties. *Värnhem s Hospital* is a hospital for chronic diseases and *Malmö Östra Hospital* is a mental hospital.

The pathology department of Malmö General Hospital provides service for the entire city In 1969 the post mortem examination rate was 91 Between 1965 and 1969 autopsies were performed on 92 / he 75 males who died in their fifty-fifth year Sernby personal communications).

The studied population

The population was selected with the aid of the County Council in Malmö, which is obliged to keep reliable and current statistics regarding the inhabitants of the city The group consisted of all men born in an even-numbered month in 1914 (*i.e* February April, June, August, October and December), and residing in Malmö at the time of the investigation.

The Malmö investigation chose men aged 55 in order to make a comparison with a Gothenburg study where men born in 1913 were examined in 1963 and again in 1967 when they were 54 years old (Tibblin 1970)

The total group consisted of 809 men when selection was terminated in November 1968 They were requested to participate in a combined health examination and population study on a specified date. Information about those men who were not able to be present at the examination was collected *to the greatest possible* extent through letter-questionnaires, telephone interviews, hospital dossiers, and visits.

The studied population is presented in Table 1 Of the 809 persons summoned 703 (87 %) appeared at the routine examinations presented in Table 3 in the next chapter The examinations were carried out at the Department of Clinical Physiology Värnhem s Hospital. Useful information was obtained from another 64 persons. Of the original population 42 men (5 %) were not included in any kind of interview or examination Table 2 shows a comparison of the

Table 1 Extent of participation of 809 men in Malmö born 1914

	n	%
Selected material	809	100
Full participation in the population study	703	86.9
Limited participation (home visits, interviewed by telephone, hospital dossiers)	64	7.9
Non-participants	42	5.2

group who took part in the scheduled examination with the 64 persons who were surveyed in another ways.

Definitions of the diagnoses provided in Table 2 are presented in the next chapter Of the group, 13 were invalid pensioners 12 of them took part in the population study They were pensioned on account of psychic or somatic disease leading to total incapacity for work. Only one of the 12 was retired because of cardiovascular disease.

Eighteen of the 809 men were of foreign extraction but had resided in Malmö for many years they did not differ from the rest of the population concerning leg blood flow

DISCUSSION

Generally speaking the degree of arteriosclerosis is higher in males than in females aged below 70 in all parts of the arterial system with the exception of the cerebral arteries, where sex and age variations are not so marked (Sternby 1968). It is therefore important to isolate the effects of sex and age when applying epidemiology to the study of arteriosclerosis.

Differences due to sex and age had no influence on the results of this study because the material was age- and sex-specific.

The individuals were contacted by telephone a few days before the decided date for the examinations. At that time, an effort was made to persuade them to participate in the study In this manner it was usually possible to examine the individuals within or quite close to their birth month. In effect, this practice resulted in the structure of a population with a mean age of 55 years ± 1 month.

The results derived from this population study would not have been valid if the number of participants had been too small. There is a great risk that the individuals who do not appear at the examination form a special group differing in some consistent way from the rest of the material

The 1963 Gothenburg population study was of men born in 1913 (Tibblin *et al* 1965 Tibblin 1967) 88 % of the 973 selected (hospital group) attended the preliminary examination. Four per cent were examined at home. Eight per cent did not take part. A comparison between the hospital examined group the home-group and the non-participant group (Tibblin 1966) revealed that

Table 2. Comparison between full and limited participation.

	Full participation = 703 (86.9 %)		Limited participation = 64 (7.9 [illegible])	
	n	%		
Previously hospitalized (any reason)	449	63.9	37	57.8
Previously hospitalized (because of myocardial infarction)	10	1 4	0	0
Angina pectoris (questionnaire)	42	6.0	3	4
Intermittent claudication (questionnaire)	20	2.8	2	[illegible]
Diabetes mellitus	12	1 7	2	[illegible]
Cancer	8	1 1	1	
Chronic bronchitis (questionnaire)	47	6.7	5	[illegible]
Smokers	436	6..0	11	[illegible]
Invalid pensioners	12	1 7	1	[illegible]

the latter differed from the other groups socio-economically Those who failed to take part had a lower average annual income and evidenced alcoholism to a larger extent than the other groups. The percentage of men who did not appear at the examination in the present study agrees almost exactly with that reported in Gothenburg. No exact survey of the socio-economic differences between those who took part and those who did not take part in this investigation has been performed. Judging from the Gothenburg-results we may postulate that such differences existed also in this population.

The 42 persons who took no part whatever in the present investigations had, on the average, been previously hospitalized to the same extent as the other subjects, but had been sick reported a little more often.

The purpose of the present report is among other things to relate calf blood flow to the prevalence of intermittent claudication myocardial infarction, and diabetes mellitus. The prevalence of these symptoms and diseases was essentially the same in those who were examined and in the 64 persons from whom information was gathered in other ways. There was no difference between their smoking habits, a fact of great importance in the present study

Useful information has been obtained regarding approximately 95 / of the selected material. Even if certain socio-economical differences may have existed between members of the examined group and those individuals who did not take part in the examination the 87 / who came to the examinations were considered representative of 55-year-old men.

3 METHODS AND DEFINITIONS

METHODS

This chapter provides a description of the methods applied to the *population study*

A thorough *follow-up study of the peripheral circulation* was carried out on subgroups selected from the original material, and the methods applied to this study will also be described.

Procedure of investigation

Four individuals were examined every weekday from January 1969 through January 1970 In Sweden July is the most common holiday month thus no examinations were carried out between June 25 and August 8, 1969 The subjects had been asked to fast from food, drink, and tobacco beginning at midnight before the examination, which began at 7.30 a.m. (see Table 3)

Examinations were initiated by general information for 10 to 15 minutes, while the subject was resting in sitting position. The sitting blood pressure, the weight, and the standing height were measured, and then the subject continued to the next station, where ECG was recorded. Lung function was examined, followed by sampling sputum for cytology and venous occlusion plethysmography Heart and lungs were X-rayed After a light meal, the subjects were interviewed and examined. The physical examination comprised auscultation of the heart and lungs, palpation of peripheral pulses, abdominal status, and rectal examination In most cases, the entire examination was completed by approximately 11.30 a.m.

Table 3 Routine examinations.

Blood pressure (sitting)
Blood tests (cholesterol, triglycerides, haematocrit)
Height
Weight
ECG
Lung function (spirometry nitrogen wash-out)
Sputum cytology
Heart-lung X-ray
Calf blood flow (venous occlusion plethysmography)
Interview (questionnaire)
Physical status (examination)

Questionnaire

The questionnaire which was used in order to obtain the personal and family medical histories — including smoking habits, bronchial symptoms, physical activity and stress—also solicited information about cardiovascular symptoms. The *cardiovascular questionnaire* was originally composed by a WHO committee and was then validated at the London School of Hygiene and Tropical Medicine (Rose 1962, Rose and Blackburn 1968). A Swedish translation was used in this present investigation The questionnaire was the same as that used in the population study in Gothenburg of men born in 1913 (Tibblin *et al* 1965).

The subjects were assigned to one of three groups according to their *smoking habits* (1) those who had *never smoked* (criterion less

than one cigarette per day for less than a year) (2) *ex smokers* comprising individuals who had stopped smoking at least one month before this investigation after having smoked regularly and (3) *smokers* This latter group was sub-divided into inhalers and non inhalers. Tobacco con sumption was quantified as follows

1 cigarette = 1 gm tobacco 1 cigarillo = 2 gm 1 cigar = 5 gm.

Pipe tobacco consumption and the approximate total amount of tobacco consumed was given in gm/day On these bases, the smokers were then assigned to one of three groups corresponding to a daily consumption of 1—14 gm, 15—24 gm or 25 gm and more

One year after the survey 100 of the previously examined individuals were randomly selected and interviewed again regarding their smoking habits. These new responses and the original ones were almost identical in 90 / of the cases with the greatest changes being no more than about ±2 gm Changes in tobacco consumption greater than 5 gm were evident in only 2 / of the cases.

A careful history of *physical activities* was taken for each participant. Subsequently subjects were grouped according to *spare-time* and *occupational activity* as described by Wilhelmsen (1969).

In order to quantify the occupational activity every individual was requested to describe the different kinds of work he did during a typical work day The lifting and carrying of heavy objects (10—20 kg and more) were noted as were sitting and moving times Spare-time activities included method of transport to and from work and were tabulated in the same way Occupation during evenings and days off was noted Participation in sport activities and the duration and intensity of such participation was also recorded Once acquired this information made it possible to divide the material into four groups according to spare-time, and occupational activities (Table 4) The amount of physical activity during the following periods of life was recorded for each subject age 20—29 30—39 40—49 50—54 and during the last year

A rough estimate of the occurrence of *psychic stress* was obtained with the aid of a combination of questions (Wilhelmsen 1969) The subjects were asked whether they were troubled by such things as uneasiness, nervousness, and anxiety and whether these were associated with economic problems, family problems, disease or problems

Table 4 Group assignment according to occupational physical activity (A) and spare-time physical activity (B) (according to Wilhelmsen, 1969)

A *Occupational physical activity*

Group I	Group II	Group III	Group IV
Predominantly sedentary sitting: desk worker watch maker sitting assembly-line worker (light goods) etc.	Sitting or standing, some walking: cashier general office worker light tool and machinery worker foreman, etc.	Walking, some handling of material mailman, waiter construction worker heavy tool and machinery worker etc.	Heavy manual work lumberjack, dock worker stone mason, farm worker ditch digger etc.

B *Spare-time physical acti ity*

C oup I	roup II	Group III	Group IV
A os mpletely inactive atching.	physical activity t least 4 hours per ding bicycle or work walking or nh the family gar etc	Regular activity such as heavy gardening, running, calisthenics, tennis, etc.	Regular hard physical training for competition in running events, soccer racing, European handball, etc., several times per week

at work. The participants, according to their responses, were assigned to six groups, corresponding to increasing psychic stress. Group I comprised individuals who could recall no periods of stress, and group VI of individuals who claimed to have had continuous stress during the past five years.

Blood pressure measurements

The recommendations from WHO were followed (Rose and Blackburn 1968). All blood pressure measurements were made by the author with the subjects in the sitting position. The mercury manometer was used throughout. Measurements were made in the mornings between 7 45 and 8 15 The room temperature was kept constant during the year at 23—24°C. After 10—15 minutes spent on routine information while the subject was seated, a blood pressure cuff with a rubber bladder 12 cm wide and 26 cm long was placed on the right arm. Systolic and diastolic blood pressures were recorded to the nearest 5 mm Hg. The systolic blood pressure was noted as the pressure read on the manometer at the auscultation of the first sound, and the diastolic (phase 5) recorded as the observed pressure when the sound had disappeared entirely

Pulse palpation

Bilateral simultaneous pulse palpation was done routinely at the carotid femoral, posterior tibial and the dorsalis pedis arteries. The results were recorded only as positive or negative.

Height and weight

Height and weight were determined according to the recommendations of WHO (Rose and Blackburn 1968). The subjects were examined while unclothed except for undershorts.

The weight was determined to the closest 0 1 kg with a lever balance

The height was measured to the nearest 0.5 cm while the subjects were without shoes and with their heels, hips, shoulders, and backs of their heads in contact with the wall and eyes looking straight ahead.

Electrocardiographic examination

Electrocardiograms were made by a skilled laboratory assistant while the subject was recumbent and had been so positioned for about 5 minutes. A direct writing recorder (Mingograph 42 B Elema-Schönander AB Sweden) was used and four leads were recorded simultaneously The paper speed was 50 mm/sec. Leads I II III aVR, aVL, aVF V_1 V_2, V_3, V_4, V_5, and V_7 were recorded. The electrocardiograms were interpreted according to the Minnesota code (Blackburn *et al* 1960) and always by the same skilled researcher [1] who had no information about the individual. A random selection of these records were examined by a second interpreter who was employed by WHO Comparison of both sets of interpretations revealed 94 / agreement.

Heart volume

The heart volume was determined with the subjects standing, according to the method described by Jonsell (1939). The X-ray pictures were inspected by an experienced roentgenologist [2] who had no other information regarding the individuals. Absolute and relative heart volumes were given in ml. The relative heart volume was given in ml/m² body surface area.

Venous occlusion plethysmography

The calf blood flow at rest and also during reactive hyperaemia was determined with venous occlusion plethysmography A water-filled plethysmograph was used and the apparatus and technique were essentially those of Dahn (1965)

The plethysmographic examination was performed on both legs simultaneously with the subject in the recumbent position. First, the arterial systolic blood pressure of the thigh was recorded plethysmographically through the use of blood pressure cuffs around the thighs

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[1] Janos Olajos, M.D
[2] Grete Iversen, M.D

directly above the knee. Thereafter the calf blood flow at rest was recorded. Then, reactive hyperaemia was achieved by obstructing arterial inflow to the legs for 3 minutes with the thigh cuffs. The blood pressure cuffs were connected to special pressure tanks which made it possible to fluctuate the pressure quickly from that adequate to occlude veins only to a pressure sufficiently great to occlude both arteries and veins. By thus alternating pressures, several flow peaks were obtained reflective of duration of hyperaemia.

The volume of the plethysmograph was 3,350 ml. The diameter of the piston recorder (F Palmer London) was 30 mm The room temperature was maintained between 23 and 24 C. The temperature of the water in the plethysmograph was 34 C During recording the arterial inflow to the foot was stopped with a blood pressure cuff placed around the lower leg, immediately distal to the plethysmograph.

The following variables were recorded routinely:

(1) *arterial systolic blood pressure of the thigh* (measured plethysmographically)

(2) *rest flow i.e the calf blood flow at rest*

(3) *blood flow* in the calf *during reactive hyperaemia*

  (a) *first flow i.e* the first measured blood flow in the calf after 3 minutes of arterial occlusion when the pressure of the thigh cuff was momentarily changed from arterio-venous to venous occlusive pressure *Results presented in this work were mainly based on first flow*

  (b) *peak flow i.e* the maximum blood flow recorded during reactive hyperaemia

(4) the *time interval* in seconds between first flow and maximum flow.

(5) *pulse ampl[illegible]udes* in mm during the peak flow

(6) *pulse rate* [illegible]

All variables e[illegible] he arterial systolic blood pressure of the thi[illegible]e recorded twice

[illegible]e pulse amplit[illegible] re measured according [illegible]ethod of Da[illegible] thout optic enlarge [illegible] f the ple[illegible] ram and without correction for leg volume A pulsation of 3 mm corresponded to a volume change of approximately 800 mm³ (Fajgelj *et al* 1967). The flow values were given in ml /min./100 ml. leg volume

Immediately following the plethysmographic examination and while the patient was still recumbent, the arterial systolic and diastolic blood pressures in the right arm were recorded The method described earlier was employed except for the changes in position The arm blood pressure was measured only once.

In this study the mean blood pressure has been calculated from diastolic arm blood pressure plus 1/3 of the pulse pressure (Folkow *et al* 1958).

Plasma cholesterol and triglycerides

Plasma cholesterol concentration was determined according to the method described by Pearson *et al* (1953) and Boy *et al* (1969) The cholesterol data were given in mg/100 ml.

Plasma triglycerides were estimated according to the method of Laurell (1966) and Kessler (1967) and were given in millimoles.

A comparison was made between cholesterol and triglyceride determinations from 25 randomly selected plasma samples as done in our own laboratory and in the Clinical Chemical Laboratory of the Sahlgrenska Hospital Gothenburg, which considers itself to be standardized with the Communicable Disease Centre Atlanta, Georgia USA (Cooper 1965) A systemic variance existed regarding results from the two laboratories. Our laboratory averaged about 50 mg/100 ml lower cholesterol, and 0.4 millimoles higher triglyceride values These differences were statistically significant ($p < 0.001$).

Lipoprotein-electrophoresis

Lipoprotein-electrophoresis was carried out on a randomly selected subsample comprising 10 % of the population. All the blood samples were taken in June after other aspects of the population study had been completed Samples for electrophoresis were taken under the same

conditions as was the blood for other analyses done in this study The electrophoretic examination was performed through argaros-gel-electrophoresis (for literature, see Houtsmuller 1969) 1 / argarose and 0 075 M barbital buffer (pH 8 6) were used. After the fractions had separated the gel was immersed for 45 minutes in methanol and water (1 1) to precipitate the fractions before drying and staining (Sudan black)

The interpretation of all lipoprotein-electrophoreses were made by a physician trained in this field.[1]

Follow-up examination regarding the peripheral circulation

On the basis of the described measurements of the calf blood flow and in accordance with the criteria stated in chapter 4 of this report, the subjects representative of the upper (n=34) and lower (n=33) 5 / of the total material in regard to quality of peripheral circulation were identified and called for a second examination. This investigation was carried out during spring 1970 immediately after the population study was concluded. At the same time, all who had been diagnosed as intermittent claudication (n=20) according to their responses to the questionnaire previously described were subjected to a special questionnaire that repeated the earlier questions concerning intermittent claudication After the second questionnaire had been critically assessed the data resulting from examination of circulation in the legs were carefully analysed Existence of any other symptoms and previous diseases was noted. Symptoms involving the loins and the joints aroused special interest.

Thereafter the following routine examinations were carried out

Physical status, including inspection of the skin with special regard to any possible trophic changes and varicose veins and perforant insufficiency

Pulse palpation was done essentially as before. Pulses were palpated in the femoral artery the tibial posterior the dorsal pedis, and the popliteal artery

Auscultation with stethoscope was done from the umbilicus to the inguen, the inguinal region, the medial side of the thighs, and the popliteal space Auscultation was also carried out over the subclavian and carotid arteries.

Back status and neurologic status, including examination of the patellar and Achilles tendon reflexes and Lasègue s test, were made routinely on all subjects.

The sitting blood pressure was measured on both right and left arm but otherwise identically with the initial examination

Lipoprotein-electrophoresis and *serum-electrophoresis*

Venous occlusion plethysmography was performed as earlier described and by the same laboratory assistant.

A *walking test* was done according to Lund (1956). The subject was requested to walk on a level linoleum-covered floor in a wide hospital corridor The walking speed was 100 paces/minute. The patient was dressed in his own clothes, without a jacket, and with shoes on. The distance walked before the appearance of symptoms is referred to as the "symptom-free walking distance The walk continued for 1000 meters or until stopped by pain. The total walking distance was recorded Walking tests were supervised by a laboratory assistant who had no information about the patient.

The *exercise test* was carried out principally according to the method described by Wahlund (1948). The test was made while the subject was seated and pedalling a bicycle ergometer (Monark-Crescent AB, Varberg, Sweden). The test began with two minutes pedalling at 300 kpm, followed by two minutes at 600 kpm thereafter work load was increased to 900 kpm if necessary The test was designed to increase the heart rate to about 150 beats per minute As soon as this heart rate was equalled or exceeded, the test was terminated The test was broken off before the mentioned heart rate if the subject suffered from angina

[1] Anders Grubb, M.D

pectoris or dyspnoea or if the ECG reaction indicated the need for this. When symptoms of claudication caused premature termination of the exercise test, arm ergometry was substituted. Electrocardiogram, blood pressure, and breathing frequency were recorded during the test at the following times

(a) before the exercise
(b) *every second minute during the exercise*
(c) immediately after the exercise
(d) 5 minutes after the end of the exercise.

All the electrocardiograms were coded according to the Minnesota code by the same researcher who had interpreted the resting electrocardiograms made in connection with the population study[1]

Statistical analyses

Frequency distributions, means, ranges, correlation coefficients, and multiple regression analyses were calculated by computer The significance of mean differences in quantifiable variables among groups was determined by the application of Student s t-test.

Chi-square was used to examine for the significance of differences among groups in regard to the distribution of values representative of a qualitative variable, except where there were low frequencies, in which condition a bionomial test was employed

In this report statistical significance (p) was tested at the 0 05 0 01 and 0.001 level.

The levels of significance are identified as
= $0.01 < p < 0.05$
$0.001 < p < 0.01$
p 0.001

I ... e tated statistical comparisons ... en a single group and the total ... ate

Symbols

n = numb
m = mean
SD = standar

Janos Olajos, M

DEFINITIONS

The following terms are defined as used in this study

Hospitalized myocardial infarction This term applies to 10 subjects previously hospitalized because of acute myocardial infarction, and they fulfilled the following criteria

(1) appearance of a pathological Q-wave and/or appearance or disappearance of localized ST-elevations followed by T wave inversions in one or several of the 12 leads

(2) two SGOT values of 55 units or more with the maximum appearing about 24 hours after the beginning of symptoms.

All the subjects had evidenced typical infarction pains according to the criteria formulated by WHO (Rose 1962).

Cerebrovascular disease This term describes five subjects, three of whom were previously hospitalized Two of these three were being treated for cerebral haemorrhage with hemiplegia and aphasia the third had had his condition diagnosed as cerebral thrombosis (Wallenberg s syndrome). Both the other subjects, although not previously hospitalized had typical medical histories of hemiplegia and dysarthria. One of them continued to evidence some weakness in one arm and was slightly dysarthric even though about a year had elapsed since his initial illness. The other showed no symptoms and was several months beyond his first episode

Diabetes mellitus Eleven members of the study claimed to have diabetes mellitus. In ten of these the diagnoses were verified by hospital records or in doubtful cases with supplementary oral glucose tolerance tests. The eleventh subject was found to have renal glucosuria. Two other individuals evidenced glucosuria subsequent oral glucose tolerance tests established that both had diabetes mellitus. Thus, twelve subjects were found to be diabetic.

DISCUSSION

In this study the recent recommendations of WHO were used in the epidemiological invest

tigations of heart and vascular diseases (Rose and Blackburn 1968).

Concerning the cardiovascular questionnaire, it is essential that the original meanings of the questionnaire terms survive translation to another language. Although this requisite is fulfilled, the questions might receive varied interpretations owing to individual differences in level of education, power of concentration, intelligence, and background experience Angina pectoris has not been identified as an important risk factor for myocardial infarction (Epstein 1965 Simborg 1970) The reason for this paradox is perhaps in part the inability to adequately diagnose angina pectoris by questionnaire. In view of this, we might question the true relation between intermittent claudication, as diagnosed by questionnaire, and the presence of arterial insufficiency of the lower extremities.

The cholesterol and triglyceride data were determined with methods used routinely in our laboratory Analyses thus done deviated considerably from duplicate sample analyses provided by the reference laboratory These deviations, however were systematic. A correction factor was neither introduced nor considered necessary as a consistent method was used in the studied material.

Several of the studied variables are known to vary during a 24-hour period. This has been amply discussed by Tibblin (1967), among others, who pointed out that blood pressure, electrocardiogram, and heart volume can change during the course of the day Strict adherence to a time schedule for all examinations from subject to subject eliminated such diurnal variations as sources of error

However it was not possible to eliminate seasonal variations as sources of error The examinations went on for more than a year except for the warmest period summer 1969 The lipid data varied with the season in the way described by Carlson and Lindstedt (1968) The cholesterol was lowest during early summer and triglycerides were lowest during autumn.

There were no discernible seasonal variations in the variables recorded plethysmographically

Recommendations by WHO concerning measurements of blood pressure were followed (Rose and Blackburn 1968). Despite this, other factors could influence the obtained values rendering it difficult to make valid comparisons with results from other investigations. One such factor is smoking. It is known that blood pressure rises in connection with smoking (Shepherd 1963). Therefore it was considered essential to know before making cross-study comparisons, whether the subjects had smoked before blood pressure measurement, and if so, how long had elapsed between smoking and measurement. Several authors, Lundman (1966) among them, have found that smokers have lower systolic and diastolic blood pressures than non-smokers. The reason for this, Lundman claimed, was that the subjects had abstained from smoking for some time before the examination. Tibblin (1967) believed that the slightly lower blood pressure in smokers is caused by their smaller amount of body fat than that of non-smokers.

Venous occlusion plethysmography is considered the best method for evaluating the circulation in the extremities in man (Graf and Ström 1959 Greenfield 1960, Hyman and Winsor 1961 Shepherd 1963 Dahn 1965, Fajgelj *et al* 1967 Bollinger 1969).

The method used by the author was essentially the same as that described by Dahn (1965) and Fajgelj *et al* (1967) Occlusion of the arterial inflow to the extremity causes reactive hyperaemia when the stasis is released (Bollinger 1969 Shepherd 1963) During reactive hyperaemia, the arterial vascular bed below the cuff is considered to be almost maximally dilated. Three minutes of arterial occlusion has been considered sufficient to produce this dilating effect (Dahn 1965 Bollinger 1969) which has been ascribed to vasoactive metabolic substances. After the period of reactive hyperaemia the magnitude of the flow is reduced especially if there is a reduction of the arterial lumen (Shepherd 1963)

Other authors have found that occlusion plethysmography agrees well with angiography in terms of identifying arterial diseases (Dahn 1965 Fajgelj *et al* 1967) Furthermore, with occlusion plethysmography it is possible to rather accurately determine whether or not stenoses or occlusions exist in the femoral region.

An important reason why venous occlusion plethysmography was used in the present study is that its reliability is well-documented. Also availability of the method played a part in its selection Venous occlusion plethysmography has been the standard method for evaluating extremity circulation for several years at the Malmö General Hospital (Fajgelj *et al* 1967).

SUMMARY

The methods used in connection with this population study conform to the recommendations of WHO were routine methods at the supporting institution, or had been tested in connection with the present study The methods have not been changed during the course of the research. Examinations were performed by experienced technicians. The author took part in, and supervised the investigation of every subject.

4 RESULTS OF VENOUS OCCLUSION PLETHYSMOGRAPHY

As earlier stated, venous occlusion plethysmography is considered the best method for evaluation of the circulation in the extremities of man. Previous investigations have revealed a relatively good agreement between angiographic findings and findings obtained with venous plethysmography (Dahn 1965, Fajgelj *et al* 1967).

Table 5 Reasons for exclusion of 19 out of 703 subjects from examination by venous occlusion plethysmography

Amputated (arteriosclerotically caused gangrene)	1
Arthrodesis or contracture of foot or knee joints	3
Refusals	15
Total	19

Number of individuals examined with plethysmography

Venous occlusion plethysmography was carried out satisfactorily in 684 of the 703 subjects who participated fully in the population study 19 were not examined (see Table 5)

One of the unexamined 19 had had his left leg amputated shortly before this study began

Table 6 Precision of measurement of different flow variables achieved with venous occlusion plethysmography

		Systolic blood pressure (thigh)	Amplitude	Rest Flow	First Flow	Peak Flow	Sec. to Peak Flow
Comparison between 2 consecutive examinations. N of legs = 20	Mean	–	–	1.8	21.0	29.4	5.6
	Mean difference	–	–	−0.03	−0.33	0.37	5.62
	SD difference	–	–	0.11	3.59	4.56	2.49
	Coefficient of variation (%)	–	–	4.4	12.1	11.1	31.8
Comparison between 2 examinations performed with 2 months interval. No of legs = 20	Mean	137	8.1	1.9	23.3	31.3	5.4
	Mean difference	8.50	0.30	±0	−0.94	−0.29	−1.00
	SD difference	11.93	2.47	0.60	3.81	6.55	2.67
	Coefficient of variation (%)	6.2	21.9	22.6	11.7	15.0	35.3

because of thrombosis of the femoral artery with complicating gangrene A preoperative plethysmography showed arterial obliteration of the right femoral artery also The other unexamined 18 had normal pulses at palpation showed no symptoms of intermittent claudication, and their smoking habits and blood lipids did not differ from those of the examined subjects.

Precision of the method

The precision of measurement of different variables achieved with venous occlusion plethysmography was tested in two ways. A comparison was made between two consecutive examinations at the same impaction of the same subject and also between duplicate examinations with approximately two months intervening. Table 6 records the results (page 19)

The precision, expressed as coefficient of variation, was best regarding first flow and peak flow after 3 minutes of arterial occlusion (Table 6). When testing the results obtained with 2 months intervening, the highest measured flows on each of the two examinations were compared. Consequently these means differ somewhat from the means of the examinations performed consecutively

Table 7 Results of venous occlusion plethysmography various authors, same method.

Author	Total number of legs	Sex	Age	Systolic blood pressure (thigh)
Dahn, I (1965) (Mean ± SD)				
Clinically healthy arteries	52	Male	45.9 ± 22.5	143 ± 27.6
"	52	Female	44 7 ± 23.9	140 ± 25.6
Legs with angiographically arterial changes but no obliteration	22		58 1 ± 8.54	123 0 ± 30.3
Legs with angiographically obliterated arteries	46		58.2 ± 9.82	97 6 ± 23 6
Fagrell, A et al (1967) (Mean and Range)				
Legs with angiographically no changes	20	Male and Female	Various	167 (95 – 40)
Moderate arteriosclerosis	7			166 (120 220)
Extensive arteriosclerosis	8			153 (110 215)
Legs with obliteration	35			161 (80 250)
Present series (Mean ± SD)	1368	Male	55	142 ± 23 5

D.m. = Different method

Comparison between previous examinations with the same method

The plethysmographic method employed in this study was essentially the same as described by Dahn (1965) and Fajgelj *et al* (1967) who used a venous occlusion plethysmograph with a water-filled system and measured the flows during reactive hyperaemia after 3 minutes of arterial occlusion. The plethysmographic results of their work are compared with those of this study (Table 7).

Dahn found somewhat higher first flows and peak flows during reactive hyperaemia in middle-aged men with clinically healthy vessels than those reported by the author of this present study This may be explained by the fact that Dahn s material consisted of subjects with clinically healthy vessels, whereas those investigated in this study had both healthy and diseased vessels. Dahn reports about the same systolic thigh blood pressures as seen in the present study but noted obviously higher rest flows.

Both Dahn (1965) and Fajgelj *et al* (1967) made comparisons between angiographic and plethysmographic findings. They found that the flows during reactive hyperaemia, *i.e* first flows and peak flows, were very much reduced if

Amplitude	Rest Flow	First Flow	Peak Flow	Seconds to Peak Flow
D m.	3.16±1.54	23 6±8.09	28.8±8.00	–
D.m.	2.87±1.12	19.0±6 64	24.3±8.49	–
D.m.	3.01±1.05	12.7±7 72	16.5±6.87	–
D.m.	3.36±1.37	5 41±2.96	10.8±4 64	–
4 7 (3–9)	2.9 (0.6–4 7)	27.3 (13 7–40.3)	28.9 (17.2–40.6)	4.8 (0–15)
3.8 (2 2–7 0)	3.03 (1 1–5 4)	18.0 (6.6–23.0)	24.4 (21.3–35.8)	10 7 (0–30)
2.3 (1–3 4)	3 98 (2.2–7.0)	15.5 (5.0–25.4)	20.7 (9 7–27.2)	15 (0–30)
1 4 (0 2 6)	3.16 (0.5–7.2)	7.8 (3.5–13.5)	13.5 (5 1–23.1)	4 (0–112)
7.5±2.3	1.9±0.7	20.7±6.4	25.8±8.6	4 4±3.3

there were arteriosclerotic changes in the absence of obliterations. If there was obliteration, the reactive flows were even further reduced. But rest flows were approximately the same in normal persons and in those with diseased vessels.

Plethysmographic criteria of arterial occlusion

In cases where arterial occlusion can be demonstrated angiographically Fajgelj *et al* (1967) have shown that the following criteria are met.

(1) amplitude ≤3 mm, and simultaneously

(2) first flow during reactive hyperaemia ≤14 ml/minute

(3) peak flow during reactive hyperaemia ≤17 ml/minute.

In the present study the subjects who fulfilled these three criteria were considered to have an occlusion or a nearly occluding stenosis within the iliofemoral arteries. These subjects have also been examined angiographically with the exception of one who died immediately after the study and where the diagnosis was verified at autopsy

Choice of discriminating variable

Investigations performed by other authors have shown that the first flow is the variable best discriminating between individuals with healthy and diseased vessels (Dahn 1965, Fajgelj *et al* 1967 Bollinger 1969). In the present study it was considered necessary because of the number of subjects, to base assignment into groups on a single variable. Initially an analysis was made of first flow and peak flow in the entire group. However in view of the earlier research cited above, it was decided to form normal and diseased groups on the basis of first flow alone. Nonetheless, it should be noted that the correlation between first flow and peak flow was good (r = 0.80)

The dependence of first flow on other variables

Statistical analyses showed that among the investigated variables first flow was significantly related to systolic and diastolic arm blood pressure and to the pulse frequency measured in connection with the plethysmographic recording. Furthermore, there was a significant negative correlation between height and first flow. Table 8 records the correlation coefficients.

Table 8 Correlation coefficient between first flow and other variables, n = 684

	First flow
Systolic blood pressure	0.31
Diastolic blood pressure	0.25
Mean blood pressure	0.28
Pulse rate	0.15
Height	−0.21
Weight	−0.07

= $p < 0.001$

The strongest correlation was between first flow and systolic blood pressure. The correlation between first flow and weight was not statistically significant.

The influence of blood pressure, pulse rate, and height on first flow has been assessed statistically with analysis by multiple regression. Although the strongest correlation was between systolic blood pressure and first flow the mean blood pressure was used to calculate regression coefficients, because this is considered to be the driving pressure. Through these calculations it was possible to construct the following prediction equation

first flow (dependent) = pulse frequency × 0.05 + mean blood pressure × 0.10 − height × 0.18 + 38.33

The multiple correlation coefficient was 0.35

This equation was used to predict the first flow for each individual resulting in standardization of the influence of pulse frequency mean blood pressure and height on the observed first flow

The observed first flow was then compared with the predicted first flow [1] In all cases, the

[1] Example of estimation of predicted first flow Individual A with pulse frequency 70 min., mean blood pressure 100 mm Hg height 180 cm. Predicted first flow equals 70 × 0.05 + 100 × 0.10 − 180 × 0.18 + 38.33 (= 19.4 ml/min.)

highest first flow in the leg with the poorest circulation was considered observed first flow Double determinations were made. The observed first flow was divided by the predicted first flow and the resultant quotient was multiplied by 100·

$$\frac{\text{observed first flow}}{\text{predicted first flow}} \times 100$$

This index was calculated for every subject and, throughout this report, is referred to as the *flow capacity* There proved to be no significant correlation between flow capacity on one hand and mean blood pressure, height, and pulse frequency on the other

Fluctuations in blood pressure during plethysmographic recording

Fluctuations in blood pressure during the recording of the flows could indicate that the mean blood pressure, on which the calculation of the predicted flow was based, was not accurate For this reason, systolic and diastolic arm blood pressures were determined in 15 randomly selected subjects (1) during the last 30 seconds of arterial occlusion (determination I) (2) during the first 30 seconds of reactive hyperaemia (determination II) and (3) during the first 30 seconds following the plethysmographic recording (determination III) The last blood pressure measurement (III) coincided with the blood pressure measurement made in the subjects who underwent plethysmography

The mean difference between II and III was 2.0 ± 3.6 mm Hg. The difference was not statistically significant. A statistical analysis showed that this slight variation in mean blood pressure failed to influence the group division appreciably

Grouping of the material according to flow capacity

The assignment of the material into groups was based on *flow capacity* Thus, the influence of blood pressure and pulse frequency was eliminated, regardless of whether that influence was physiologically or patho-physiologically precipitated. In the same way the negative influence of height was eliminated.

The main principle was to assign the population into deciles (Documenta Geigy 1962) of flow capacity and this grouping is presented in Table 9 Table 9 also shows the mean magnitude of the first flow in each decile In addition to the decile groups, two other groups were formed, *extreme*-1 and *extreme*-10 These groups consist of the 5 / of the population with the lowest (extreme 1 n=33) and highest (extreme-10 n=34) flow capacities and are, in fact, representative of the poorest half of decile 1 and the best half of decile 10

The results of this study will be expressed in relation to the following subject classifications

(1) *decile-groupings* based on flow capacity with the sub-groups *extreme-1* and *extreme-10*

(2) *occlusions or stenoses* within the iliofemoral arteries, such diagnoses having been established on the basis of criteria stated in this chapter

DISCUSSION

Venous occlusion plethysmography provides recordings of several variables. Of the measured flow variables, the circulation at rest showed the weakest relation to the degree of arteriosclerotic changes (Dahn 1965, Fajgelj *et al* 1967) The same authors have also proved that there

Table 9 Flow capacity in all deciles with mean and standard deviation of first flow

Deciles	1	2	3	4	5	6	7	8	9	10
	67	68	69	69	68	69	69	68	69	68
Flow capacity	≤65	66−76	77−85	86−92	93−98	99−105	106−112	113−122	123−135	≥136
First flow m	11.9	15.6	18.1	18.8	21.0	21.5	23.9	24.6	26.8	31 1
S.D.	4 1	3.5	4.3	4.3	3.9	4 4	4.8	3.9	4 4	5.5

is a good correlation between flows measured during reactive hyperaemia (first flow and peak flow) and the degree of arteriosclerosis.

The magnitude of the flows during reactive hyperaemia can be considered a good measure of the reserve capacity of the arterial tree (Dahn 1965 Bollinger 1969).

From the epidemiological point of view it does not matter whether the first flow or the peak flow is used as the discriminating variable. Since previous investigations (Dahn 1965) found the first flow to be more strongly related to the degree of arteriosclerosis, the first flow was selected. However the correlation between the first flow and the peak flow was quite strong.

As a reflection of the morphology of the arterial tree, the first flow should form an adequate basis for a class assignment of the population, provided that the first flow is dependent upon arterial tree morphology only Our own investigations, however showed that the first flow was significantly related to the arm blood pressure, pulse frequency and height.

The relation of systemic blood pressure to the reactive flows has been studied earlier by among others Wilkins and Eichna (1941) who found that the flows varied with the amplitude of the blood pressure.

The influence of the pulse rate on the magnitude of the first flow is probably secondary to a larger cardiac output per minute in those with high pulse frequency thereby increasing peripheral flow

The explanation of the negative correlation between height and first flow is not clear Tall individuals in the upright position have a higher pressure in the lower extremities than do short ones. *This might possibly cause an adaptive* hypertrophy of the arterial wall (Folkow personal communications)

The calculation of *flow capacity* implied standardization for the influence of systemic blood pressure, pulse frequency and height on the first flow Possible patho-physiological connections between these variables and the magnitude of the first flow were thus eliminated.

The material was divided into deciles of flow capacity based on the first flow during reactive hyperaemia It was observed that when classifying according to first flow there is a tendency for subjects with angiographically healthy vessels to overlap those with diseased vessels (Dahn 1965, Fajgelj *et al* 1967) Such an overlapping was judged to be of no importance from the epidemiological point of view since those with the most advanced arteriosclerosis could be expected to belong to the group with the lowest flow capacity

Judging from autopsy studies, it seems certain that arteriosclerosis is the predominant cause of symptoms of arterial disease in 55-year-old men (Sternby 1968) It appears logical that reduced flow capacity should be evident in arteriosclerotic disease, and that the reduction could be conditioned by morphological changes in the arteries and arterioles above the plethysmograph cuff (arteriosclerotic plaques, thromboses, wall hypertrophy fibrosis, sclerosis).

SUMMARY

Of the variables measured at venous occlusion plethysmography other authors have proved that the first flow during reactive hyperaemia is the variable best discriminating between subjects with healthy and those with diseased arteries. However the first flow appeared to be significantly related to the systemic blood pressure, pulse frequency and height. The influence of these variables on the first flow was mathematically accounted for and for every subject, an index called *flow capacity* was calculated The *flow capacity* (the ratio between observed and predicted first flow) is considered an adequate measure of the reserve function of the arterial tree, thereby indirectly reflecting the possible existence of arterial disease. In this study it was accepted as a principle that among 55-year-old Swedish men the predominant cause of arterial disease is arteriosclerosis

5 VALIDATION OF THE WHO QUESTIONNAIRE AND REPORTS OF CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS RELATED TO VENOUS OCCLUSION PLETHYSMOGRAPHY

In the book *Cardiovascular Survey Methods* Rose and Blackburn (1968) established that available techniques for studying the peripheral vascular diseases are quite limited and that conventional clinical methods for evaluating peripheral pulses and peripheral circulation are not sufficiently reliable.

In this chapter an effort is made to

(1) evaluate the accuracy of the cardiovascular questionnaire in diagnosing intermittent claudication (Rose and Blackburn 1968)

(2) analyse plethysmographically diagnosed occlusion and near-occluding stenosis in the iliofemoral arteries

(3) evaluate the clinical importance of reduced flow capacity

(4) examine laboratory and clinical findings in cases of myocardial infarction cerebrovascular disease, diabetes mellitus, and occlusions in the iliofemoral arteries

(5) relate electrocardiographic findings to plethysmographic results.

RESULTS

Intermittent claudication diagnosed by questionnaire

Based the responses obtained with the aid of the ca d ovascular questionnaire, 20 subjects (8 .) were diagnosed as having intermittent claudication. These were requested to return for further investigations. Table 10 provides a description of this group and analysis of reasons for mentioned symptoms of claudication in connection with the population study In Table 10 the subjects have then been ranked from 1 to 20 according to increasing magnitude of flow capacity

A careful analysis of medical histories showed 8 of these 20 subjects to have typical symptoms of claudication. In 6 of the 8, symptoms were considered to be due to arterial insufficiency In two cases, arterial insufficiency could not be demonstrated. In one of the two cases (ID 208) Parkinson s disease and low back pain were diagnosed and the other (ID 388) had angiospastic symptoms with gouty arthritis as possible explanations for leg pains.

In two cases in the claudication group arterial insufficiency could not be excluded. One (ID 99) had a flow capacity of only 55 but showed no signs of occlusion, clinically or plethysmographically and his walking test was negative. The remaining case (ID 465) probably had a haemodynamically important aortic stenosis. His response to the walking test was pathological, but the flow capacity was relatively high

One individual (ID 174) did not meet the plethysmographic criteria for occlusion, but had moderate symptoms of claudication a pathologic walking test, and a flow capacity of 68 In this case, there were clinical signs of occlusion with no pulses from the femoral artery downwards. His moderate symptoms, in spite of severe clinical signs, might be explained by the possible

Table 10 Intermittent claudication according to WHO questionnaire. Analysis of reasons for mentioned complaints.

Identification No	Flow capacity (poorest leg)	Typical intermittent claudication		Re-examination Pulse palpation Femor	Popl	Tib. post.	Dors. ped
329	Missing data (Md)	+	R	+	−	−	−
			L	−	Amputated		
26	13	+	R	+	−	−	−
			L	+	−	−	−
688	14	+	R	+	−	−	−
			L	+	−	−	−
471	19	+	R	+	+	+	+
			L	+	+	+	+
119	50	+	R	+	+	+	+
			L	−	−	−	−
99	55	−	R	+	+	+	+
			L	+	+	+	+
174	68	+	R	−	−	−	−
			L	+	+	+	+
31	69	−	R	+	+	+	−
			L	+	+	+	−
465	73	?	R	+	+	+	+
			L	+	+	+	+
208	81	+	R	+	+	+	+
			L	+	+	+	+
327	83	−	R	+	+	+	−
			L	+	+	+	−
133	88	−	R	+	+	+	+
			L	+	+	+	+
110	89	−	R	+	+	+	+
			L	+	+	+	+
515	93	−	R	+	+	+	+
			L	+	+	+	+
436	95	−	R	+	+	+	+
			L	+	+	+	+
216	102	?	R	+	+	+	+
			L	+	+	+	+
199	108	−	R	+	+	+	+
			L	+	+	−	−
388	123	−	R	+	+	−	+
			L	+	+	−	+
325	125	−	R	+	+	+	+
			L	+	+	+	+
370	144		R	+	+	+	+
			L	−	+	+	+

A comparison was made een first flow at repeated plethysmography and the first flow on which flow capacity

(peripheral circulation)

Murmurs (iliofemoral arteries)	First flow at repeated plethysmography	Symptom-free walking distance	Explanation for complaints of intermittent claudication
–	(Md)	(Md)	Arterial insufficiency
– –	St. quo	160	Arterial insufficiency
– –	St. quo	240	Arterial insufficiency
+ +	St. quo	400	Arterial insufficiency
– –	St. quo	200	Arterial insufficiency
– –	St. quo	1000	Calf pain at rest and when walking. Pes planus. Varicose veins. Arterial insufficiency
– –	St. quo	950	Arterial insufficiency
– –	–	1000	Pains in lower legs at rest and when walking. Aetiology uncertain.
– –	St. quo	760	Aortic stenosis. Arterial insufficiency
– –	+	560	Parkinson's disease. Low back pain.
– –	+	1000	(Did not understand the questions.) Low back pain.
– –	St. quo	1000	Low back pain.
– –	St. quo	1000	(Did not understand the questions.)
– –	St. quo	1000	Psychic symptoms. Neuralgic foot pain.
– –	St. quo	1000	Psychic symptoms. Disturbed concentration.
– –	St. quo	1000	Mental debility
– –	–	1000	Cramp of left lower leg. Disturbed sleep. Occlusion of arteries of left lower leg
– –	St quo	1000	Angiospastic symptoms in hands and feet. Gouty arthritis.
– –	–	1000	(Did not understand the questions.)
–	–	1000	Coxalgia (arthrosis deformans).

was based. Difference ≥ 2 ml min is recorded with + or –

existence of an especially good system of collateral vessels.

Low back pain, mental problems, and misinterpretation of the questions were otherwise the most common explanations of the false claudication symptoms.

Plethysmographically diagnosed occlusions in the iliofemoral arteries

Based on the plethysmographic criteria of occlusion accepted in this study the diagnosis of iliofemoral occlusion was established in 8 subjects (1 1 /) The diagnosis was verified angiographically in 7 and at autopsy in one A focused follow up study of this group yielded the results reported in Table 11

Here we find 5 of the 6 questionnaire diagnosed subjects, who were found to have intermittent claudication caused by arterial insufficiency Furthermore Table 11 describes 3 subjects who claimed to have not had any symptoms of claudication. Their absence of subjective symptoms is due in all cases to the existence of concurrent diseases which limit their ability to move. Two subjects had angina pectoris and residual symptoms after myocardial infarc tion and cerebrovascular disease. The third subject had had an operation for laryngeal cancer and had also a ventilatory insufficiency The occlusion group consisted of those with severe illnesses and their functional impairment as a rule, was not due solely to their peripheral

Table 11 Clinical status of subjects with occlusion or near occluding stenosis in the iliofemoral arteries, n = 8

Identification No.	Major diagnosis	Additional diagnosis	Intermittent claudication (questionnaire)	Pathologic walking test	Flow capacity
26	Occlusion bilat	Status post infarctum cordis	+	+	13
119	Occlusion left	Status post infarctum cordis	+	+	50
329	Occlusion bilat	Stenosis in arterie carotis amb	+	Missing data (Md)	(Md)
344	Occlusion right	Status post infarctum cordis + Haemorrhagia cerebri sequelae	–	+	50
366	Stenoses bilat	Cancer laryngis (operata)	–	+	49
471	Stenoses bilat	Morbus cordis arteriosclerocticus			19
634	Stenosis	Status post infarctum cordis – Thrombosis cerebri sequelae		+	47
6 8	Occlusion	Diabetes mellitus	+	+	14

Plethysmographic examinat few months before the population study Angiography revealed bilateral occlusion
Exercise test Minn. code 1 d angina pectoris.

vascular disease. Four of the 8 had previously had myocardial infarctions. Two others had either at rest or in exercise ECG-abnormalities indicative of coronary artery disease.

The blood pressure was determined at the follow up investigation on both the right and left arm. No differences above 10/5 mm Hg were found.

Clinical importance of reduced flow capacity

In Table 12 the material has been divided into deciles of flow capacity. The frequences are also stated for all the subjects. Myocardial infarction and cerebrovascular disease were more common in decile 1 than in the total material. Half of the subjects with diabetes mellitus were assigned to either of the two lowest deciles. There was no parallel between absence of one of the foot pulses or symmetric absence of one foot pulse and the magnitude of the flow capacity.

Both subjects with myocardial infarction, cerebrovascular disease, and diabetes mellitus were also in the deciles with high flow capacity which means that unusually good peripheral circulation can prevail in some subjects with these diseases.

Table 13 shows further comparisons between certain findings in the medical histories and the magnitude of the flow capacity. Here, the material has been divided in a way different from Table 12. Comparisons with the occlusion group

	Pulse palpation				Murmurs (ilio-femoral arteries)	ECG t rest Minn. code	Blood pressure right arm
	Fem.	Popl.	Tib. post.	Dors. ped			
R	+	–	–	–	–	1–1–4	110/80
L	+	–	–	–	–	5–2	
						6–3	
R	+	+	+	+	–	1–1–4	130/75
L	–	–	–	–	–	4–2	
						5–3	
						8–3	
R	+	–	–	–	–	0	185/95
L	+	Amputated					
R	+	–	–	–	–	4–3	225/140
L	+	+	–	–	–	5–3	
R	+	+	+	+	+	2–3	175/80
L	+	+	+	+	+		
R	+	+	+	+	+	1–3–3	170/105
L	+	+	+	+	+	3–1	
						4–4	
						5–3	
						8–3	
R	–	+	+	–	+	1–2–4	145/75
L	+	+	+	–	–	4–3	
						5–2	
R	+	–	–	–	–	0[a]	180/75
L	+	–	–	–	–		

Table 12 Medical history and pulse palpation in various deciles of flow capacity

Decile	n	Myocardial infarction	Cerebrovascular disease	Diabetes mellitus	Femor	Tib unilat.	Tib bilat	Dors. p unilat.	Dors. p bilat.	Tib. post. + dors. ped same foot
		No palpable pulses								
		n %	n %	n %	n	n %	n	n %	n %	n
1	67	4	3	3	1	3	3	8	13	4
2	68	0	0	3	1	6	3	12	4	1
3	69	1	0	1	0	3	1	8	10	0
4	69	1	0	0	0	3	3	4	8	0
5	68	1	0	2	0	2	3	11	6	0
6	69	0	0	0	0	2	1	6	8	0
7	69	1	1	1	0	3	1	5	8	0
8	68	0	0	1	0	2	1	4	10	0
9	69	1	0	1	0	1	3	4	9	1
10	68	0	1	0	0	2	3	6	6	0
Missing data	19	1	0	0	1	1	2	3	2	1
Total population	703	10 (1 4)	5 (0.7)	12 (1 7)	3 (0 4)	28 (4.0)	24 (3.4)	71 (10.1)	84 (12.0)	7 (1.0)

[1] Not examined plethysmographically
$-0.01 < p < 0.05$, $-0.001 < p < 0.01$ compared with the total material

have also been made. Seven of the 8 subjects in the group with diagnosed occlusion also belonged to the extreme-1 group. This means that if those with occlusions were excluded, the low flow capacity group would not differ from the material as a whole. In the extreme group with the best flow capacity (extreme-10), there *was no subject with any of the diagnoses* mentioned in Table 13.

In order to form an opinion of the functional importance of extremely low flow capacity a standardized walking test was given to all members of the groups extreme-1 and extreme-10. Table 14 reports the results. It includes data

Table 13 Medical history accompanying occlusion and at different magnitudes of flow capacity

Diagnoses	Occlusion n = 8		Extreme-1 n = 33		Middle group n = 617		Extreme-10 n = 34	Not examined plethysmographically n = 19	Total material n = 703	
			Grouping based on flow capacity							
			n	%	n		n	n	n	
Myocardial infarction	4	(50.0)	4	(1[illegible]1)	5	(0.8)	0	1	10	(1 4)
Cerebrovascular disease	2	(25 0)		(6 0)	3	(0.5)	0	0	5	(0 7)
Diabetes mellitus	1	(12.5)	2	(6.0)	10	(1.6)	0	0	12	(1 [illegible])
Intermittent claudication (questionnaire)	5	(62.5)	6	(18.2)	13	(2 1)	0	1	20	(7 8)
Angina pectoris (questionnaire)	4	(50 0)	6	(18.2)	35	(5 7)	0	1	42	(6 0)

$-0.01 < p < 0.05$ 0.001 $p < 0.01$ $-p < 0.001$ compared with the total material.

Table 14 Results of walking test, extreme-1 and extreme-10

	Terminated because of typical intermittent claudication	Terminated because of angina pectoris + intermittent claudication	Terminated because of angina pectoris alone	Totally	
	n	n	n	n	%
Extreme-1 n = 33	4	3	2	9	(27.3)
Extreme 10 n = 34	0	0	1	1	(2.9)

from the 7 subjects in the extreme-1 group who had earlier been given the diagnosis of occlusion. The walking test failed to provoke symptoms of claudication in subjects with extremely low flow capacity but without occlusion. Two subjects in extreme 1 had to terminate the walking test because of angina pectoris and one subject in group extreme-10 had to terminate the walking test for the same reason. This was later confirmed by exercise-ECG

Laboratory and clinical findings in myocardial infarction, cerebrovascular disease diabetes mellitus, and occlusion in the iliofemoral arteries

Table 15 shows that the flow capacity was lowest in cases of documented occlusion, but that it was also significantly reduced in subjects with histories of myocardial infarction and diabetes mellitus.

Systolic and diastolic *blood pressures* were not significantly increased with myocardial infarction, but were with cerebrovascular disease. Systolic blood pressure was significantly elevated in cases of occlusion, but diastolic blood pressure was not.

The relative *heart volume* was significantly increased in those with histories of myocardial infarction and in cerebrovascular disease.

Cholesterol and *triglyceride* concentrations were significantly increased in those with myocardial infarctions or cerebrovascular disease. Subjects with iliofemoral occlusion had a moderate increase of cholesterol and a significant increase of triglycerides. Among those with

Table 15 Flow capacity blood pressure, heart volume, and blood lipids in different diseases in the subjects.

Diagnosis			Flow capacity	Blood pressure		Heart volume		Cholesterol	Triglycerides
				Systolic	Diastolic	Total	Relative		
Myocardial infarction	10	m	73.4	150.5	87.5	1006[1]	532	287.5	2.88
		SD	36.3	36.9	22.9	278	134	65.5	3.22
Cerebrovascular disease	5	m	82.2	196.0	121.0	1150.0[1]	600.0[1]	286.0*	2.00*
		SD	41.1	24.9	13.9	176.3	115.5	40.5	2.25
Diabetes mellitus	12	m	80.3	146.7	81.3	916.7	476.7	229.6	1.30
		SD	30.4	20.9	10.7	209.3	92.5	42.2	0.78
Occlusion	8	m	34.6[1]	165.0*	90.6	965	507[1]	276.4	2.41
		SD	18.1	35.9	22.8	248	118	63.4	2.20
Total material	703	m	100.0*	138.7	83.8	885*	464*	246.6*	1.08*
		SD	28.1	22.5	14.5	174	78	43.9	0.73

Missing data for one subject Missing data for 19 subjects. Missing data for two subjects.
= 0.01 p 0.05 = 0.001 < p < 0.01 = p < 0.001 compared with the total material.

in the eighth at autopsy The prevalence of occlusions or near-occluding stenosis within the iliofemoral arteries was 1 1 %, which is probably somewhat lower than that reported by Widmer and Glaus (1970), who found an occurrence rate of 1 / in men aged 40—50 and an age-related increase to 7 / in men 65—74 years of age

In the occlusion group only 5 of the 8 subjects had medical histories of intermittent claudication. The other 3 had palpable foot pulses but auscultatory stenoses. A battery of medical history auscultation, and pulse palpation therefore could detect the disease in all of these 8 subjects.

In one, the medical history showed typical claudication and there were palpatory signs of occlusion However the plethysmographic criteria of occlusion were not met Technically unsatisfactory recording or unusually good collateral circulation seemed logical explanations for the obtained plethysmographic results. At a plethysmographic examination in connection with the follow-up investigation of the peripheral circulation this subject fulfilled the criteria of occlusion.

In the 5 / of the material with the poorest flow capacity it was not possible to demonstrate more than 8 cases of occlusion with the aid of medical history pulse palpation, auscultation and plethysmography

Therefore *the prevalence of occlusions in the iliofemoral arteries should, in 55 year-old men be very close to 1 1 %.*

Neither pulse palpation of the foot nor the questionnaire gave an adequate conception of tr rt l reserve function The walking test pro ed t alid in cases where there was oc lu o F l not provide accurate information rega u n r l reserve function in cases of extremely i capacity in the absence of occlus n C ntly it seems that overt symptoms f rc u ufficiency are delayed until advanced t total obliteration have evolved. However th w lking test may in some instances be normal even if there are occlusions angiographically (Fajgelj *et al* 1967)

Autopsy studies and clinical investigations have been made in order to elucidate the associations among arteriosclerosis in various vascular regions. Some authors have been able to prove through autopsy studies that arteriosclerosis may vary considerably from one vascular region to another (Duguid and Robertson 1955 Baker *et al* 1961). Other such studies have demonstrated the simultaneous existence of stenosis of coronary vessels and of the carotid, vertebral, and iliac vessels. This latter finding supports the concept that arteriosclerosis is a systemic disease (Mitchell and Schwartz 1962). Sternby (1968) found a rather strong relation between presence of arteriosclerotic changes in the iliofemoral arteries and in the coronary arteries. The relation was not as strong between the presence of disease in the iliofemoral arteries and in the cerebral arteries.

Clinical investigations also have been carried out to clarify the connection between arteriosclerosis of the lower extremities and of other vascular regions (McDonald 1953 Selvaag 1956 Lozada *et al* 1959 Juergens *et al* 1960 Singer and Rob 1960, Boyd 1962, Tillgren 1965 Blümchen *et al* 1966, Schütz 1967 Erdweg and Maurer 1969 Reimer *et al* 1969 Grunewald *et al* 1970) With the aid of various methods, including medical history clinical measurements, and electrocardiographic techniques, it was found that those with arterial occlusions of the lower extremities had an elevated incidence of coronary artery disease and of myocardial infarction and also a lower survival rate after myocardial infarction Furthermore people with diseases of the peripheral vessels had morbidity and mortality rate due to myocardial infarction that were in excess of such rates due to cerebrovascular disease (Singer and Rob 1960)

Several authors, such as Sternby (for literature see Sternby 1968) have found strong links between hypertension and arteriosclerosis and between diabetes mellitus and arteriosclerosis.

Hypertension and diabetes, either singly or together may accompany a distinctly increased degree of arteriosclerosis. These diseases certainly cannot be identified as the causes of arteriosclerosis, because advanced arteriosclerosis can exist in the absence of both. None the less there is little doubt that hypertension and diabetes mellitus hasten the natural course of arteriosclerosis (Robertson and Strong 1968)

In this study it was noted that half of the subjects with occlusions in the iliofemoral arteries had suffered at least one myocardial infarction. Furthermore, there was a significantly higher prevalence of ECG-abnormalities indicative of coronary artery disease in subjects with extremely low flow capacity than there was in the total material. The present study supports the theory that both clinically manifested and sub-clinical arterial insufficiency of the extremities and of the coronary arteries often co-exist. These findings argue in favour of a general spread of the arteriosclerosis.

On the other hand, we noticed that some of the subjects who had had myocardial infarction demonstrated a flow capacity equal to or even higher than that in the total material. A localized arteriosclerosis thus also appears to exist.

Some of the risk factors for cardiovascular disease have been mentioned in this chapter and are thoroughly discussed in the next chapter At this point, it should be stressed that the relatively uniform risk factor patterns that accompany diagnoses of myocardial infarction, cerebrovascular disease and occlusions in the iliofemoral arteries could be partly explained by the observed co-existence of two or more of these diseases Cholesterol and triglyceride values showed essentially the same pattern in the three diseases, whereas hypertension was more specifically concomitant with cerebrovascular disease (Bjurulf 1964) The three diseases consequently showed a relatively homogenous lipid pattern but with differences in blood pressure It is also of interest to note that the diabetes mellitus group differed hardly at all from the total material in regard to all measured variables, except for a reduced flow capacity

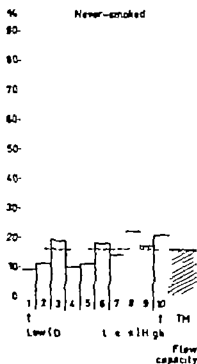
SUMMARY

Of 703 55-year-old men, 20 (2.8 %) were diagnosed as intermittent claudication with the WHO questionnaire Arterial flow insufficiency could be demonstrated in only 6 of these subjects. Three other subjects who claimed no symptoms of claudication on the questionnaire were later found to have arterial insufficiency Either occlusion or near-occluding stenosis in the iliofemoral arteries was judged to exist in 8 subjects (1 1 %). The diagnoses were made by medical history pulse palpation, and venous occlusion plethysmography with verification in 7 cases by angiography and in one case at autopsy

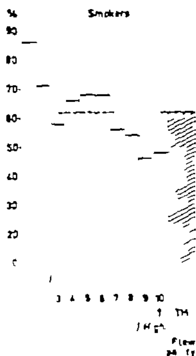
Co-existence of myocardial infarction, and/or cerebrovascular disease and/or peripheral arterial occlusion was noticed in several cases. Signs of general spread of arteriosclerosis were quite common, even though a few subjects showed more limited arteriosclerosis.

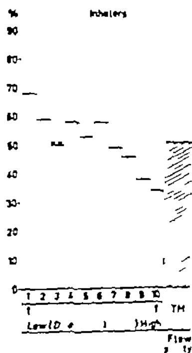
The cholesterol and triglyceride values showed a relatively homogenous pattern in subjects with myocardial infarction, cerebrovascular disease, and peripheral arterial occlusion. The highest blood pressure was noted in cerebrovascular disease.

The diabetes mellitus group did not differ appreciably in any measured parameter from the average of the total material except for a reduced flow capacity









ers in flow capacity deciles and in the total material.

significantly greater than in the total material ($p < 0.001$), and in deciles 9 and 10 the frequency of smokers was lower than in the total material ($p < 0.05$).

Inhalers were more common in decile 1 than in the total material ($p < 0.05$) in deciles 9 and 10 the frequency of inhalers was lower than in the total material (decile 9 $p < 0.05$ decile 10 $p < 0.01$).

A further analysis of the relation of smoking habits to the magnitude of the flow capacity is presented in the next chapter

Physical inactivity

a. Occupational activity

The degree of occupational activity was essentially the same among the different deciles. There was no significant difference between the extreme groups of decile 1 and 10 and the total material.

b *Spare-time activity*

An analysis of the spare-time physical activity from age 20 to 40 showed that there were no significant differences among the various deciles or between the two extreme groups and the total material. From the age of 40 onwards, there were differences which became more marked during the years just before the population study

Spare time physical activity classified as group III during the year before the population study is presented in Figure 3

Group III physical activity (regular physical activity such as heavy gardening, running, tennis etc.) was more common in the extreme group of decile 10 than in the total material ($p < 0.05$). Such a difference could not be demonstrated between any othe group and the material as a whole.

Group IV phys cal activity was indulged in by very few and there were no obvious differences among the flow-groups.

Group I and II physical activity was approximately equally frequent in the different deciles.

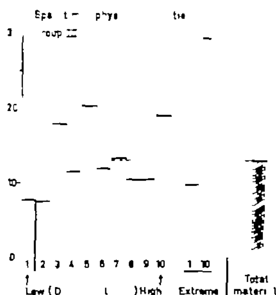


Fig 3 Prevalence rate of group III spare-time physical activities in flow groups and in the total material.

Weight

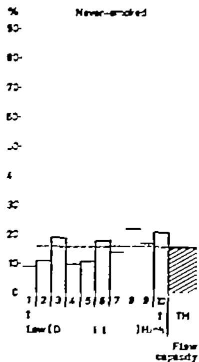
The average weight in decile 1 was about 1 kg more than in the total material. There were no significant differences between the single deciles and the total material. No attempt was made to determine the amount of fat in the subjects in connection with the study and no conclusions can be drawn regarding a possible relation between obesity and flow capacity

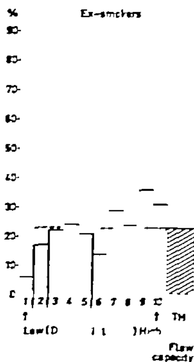
Stress

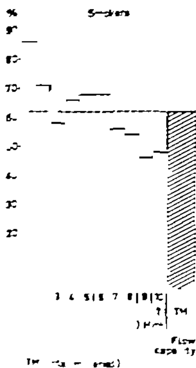
A rough estimate of the presence of stress in the different subjects was made with the aid of a questionnaire (see chapter 3). No relation could be demonstrated between the presence of stress and the magnitude of the flow capacity

Hypertension

Systolic and diastolic casual blood pressure in those with documented occlusion in the ilio-femoral arteries has been presented earlier (Table 15). The mean systolic, but not the diastolic blood pressure in these patients was significantly increased compared with that of the total material ($p < 0.001$) The mean blood







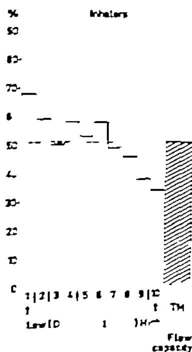


Fig Sm[illegible]g habits in flow capacity deciles and in the total material.

capacity and various smoking habits. Almost all subjects in decile 1 were smokers and most of the inhalers are found in this group as well. Decile 9 and 10 had the fewest smokers but the most ex-smokers. These findings render tobacco smoking suspect as one cause of initiating the low flow capacity in the legs. Investigations carried out by Astrup *et al* (1967) and by Kjeldsen (1969) support the concept that carbon monoxide inhaled with tobacco smoke promotes arteriosclerosis. Reports by Hess and Frost (1968) showed that smoking can also be a factor in thrombosis. Autopsy studies carried out by Auerbach *et al* (1968) identified a significantly increased fibrosis of the walls of the arterioles and small arteries with increased cigarette consumption It is apparent that smoking could directly cause arterial injuries and thereby be responsible for the observed relation between smoking and reduced flow capacity

Of those eight cases of occlusion all were either smokers or ex-smokers. A more thorough analysis regarding the relation between smoking and flow capacity is presented in the following chapter

The relation between high blood pressure and arteriosclerosis has been studied by many authors the predominant opinion is that arteriosclerosis and hypertension are different diseases, but that hypertension accelerates the course of arteriosclerosis (Stamler 1962, Sternby 1968 Robertson and Strong 1968) In the present study a statistical relation has been demonstrated between high systolic blood pressure in the arm and occlusion in the ilio-femoral arteries. This relation is expected as most members of the occlusion group had generalized arteriosclerosis. It is natural for the systolic blood pressure to be high in the presence of a rigid arterial system. The relation between hypertension and peripheral circulation is further discussed in chapter 8.

So far the relation between low flow capacity and various risk factors have been discussed. What is then significant for the subjects with the highest flow capacity? The subjects in the extreme-10 group of decile 10 (highest flow capacity) were primarily characterized by more physical activity in their spare-time. Previous investigations have shown that habitual physical inactivity is related to the incidence of coronary artery disease (Simborg 1970). Investigations regarding the relation between physical activity in spare-time and at work, on one hand, and the incidence of myocardial infarction, on the other have been carried out by Wilhelmsen and Tibblin (1971) They used the same questionnaire as was employed in the present study and found that low physical activity (group I—II) during the last year was significantly more common in those who later had a myocardial infarction than in a randomly selected group of men (53—54 years old)

Concerning the circulation in the legs, a rise in the flows during reactive hyperaemia was observed after physically training subjects with intermittent claudication due to arterial occlusion (Ericsson *et al* 1971 Fitzgerald *et al* 1971). This might be because physical training stimulates development of collateral circulation (Eckstein 1957 Sanne and Sivertsson 1968).

However plethysmographic studies have shown that the blood flow to the musculature of the working extremity is greater in trained than in the untrained subjects (Pernow 1971). Conceivably physical training can induce a more effective distribution of the available blood to the exercising muscles.

The explanation for the relation between high spare-time physical activity and high flow capacity could consequently be healthy vessels and/or possibly altered distribution of available blood during reactive hyperaemia.

The existence of multiple risk factors should also be discussed in this context. Concerning the incidence of coronary artery disease, it is known that the existence of multiple risk factors, as opposed only one, considerably augments the likelih d f coronary artery disease (Epstein 1965 Simb g 1970, Atherosclerosis study group 1970, Tibl 1970). The smallness of the group

with occlusion precludes firmness of findings, but we were able to establish that hypertension, hyperlipaemia, and smoking were all present in this group It is known that the presence of multiple risk factors (over-weight, hyperlipaemia, hypertension, and cigarette smoking) is more common among those with occlusion of the leg arteries than among those with no such disease (Widmer *et al* 1969).

With the exception of smoking, there was no relation between *low flow capacity in the* absence of occlusion and the various risk factors. Conditions were somewhat different in regard to subjects with the highest flow capacities. *In the extreme group of decile 10* there were a high frequency of subjects physically active in their spare-time, a large number of ex smokers, and a low number of smokers. Furthermore, the serum triglycerides were lower in this group than in other groups. A subsequent analysis showed that group III spare-time physical activity during the last year was more common among ex-smokers than among those who smoked ($p<0.01$) However mean triglyceride concentration of the ex-smokers as a group was not lower than that for the rest of the material. In the extreme group of decile 10, somewhat lower triglyceride values were found for group III physically active subjects than for the rest of the subjects in decile 10 Previous reports illustrate that the serum triglyceride concentration is lower in those who are regularly physically active in their spare-time, but not in those who do heavy physical work (Carlson and Lindstedt 1968). Investigations carried out by Holloszy *et al* (1964) showed that physical activity effects fat metab[illegible]m in such a way that mean serum triglyceride [illegible]centration in a mixed material of inact[illegible]dle-aged men decreased significantly af[illegible]n training period and this persisted for 48 hours. The slightly lower level of triglycerides in the group with the best flows can perhaps be ascribed to the better exercise habits adopted by members of this group. In addition, many members of the extreme group of decile 10 were ex-smokers. At the same time, ex-smokers as a group were found to be more physically active than smokers

An analysis of risk factors was performed in yet another way Cholesterol and triglyceride *levels above the median more than 14 gm* tobacco consumption per day and group I and II physical activity were considered risk factors. The number of subjects with one or more such *risk factors was calculated for each decile.* Except that the number of heavy smokers was greatest in decile 1 there were no essential differences among the deciles in terms of this analysis.

SUMMARY

In 55-year-old men, it was found that systolic hypertension, hypercholesterolaemia, hypertriglyceridaemia and lipoprotein abnormalities were clearly related to occlusive vascular disease in the iliofemoral arteries. Smoking proved to be clearly related to the magnitude of the arterial flow capacity in the legs and also to occlusive vascular disease. *Smoking may have* the ability of generally influencing the whole arterial tree. *Physical inactivity occupational or* spare time, was not related to low flow capacity but high physical activity in spare-time was correlated to extremely high flow capacity in the legs. More subjects with high flow capacity than members of deciles with low flow capacities were ex-smokers. The ex smokers were more active in their spare-time than the smokers.

In recent years, a vast literature has accumulated which overwhelmingly supports the concept of a strong relation between smoking and morbidity and mortality in ischaemic heart disease, lung cancer chronic bronchitis, emphysema, and other diseases.

A WHO report by Fletcher and Horn (1970) provides a summary of results from earlier published investigations The large prospective studies have proved clearly that (1) cigarette smokers as a group have 30–80 % higher over all mortality than non smokers (2) mortality rises with increasing cigarette consumption (3) mortality is proportionally higher among cigarette smokers between 45 and 54 years of age than at earlier and later ages (4) mortality is higher in those who began smoking in earlier years than in those who began later (5) mortality is higher among inhalers than non inhalers, and (6) mortality is lower among cigarette smokers who stopped smoking than among those who have continued.

A very strong relation has been shown between smoking and mortality in ischaemic heart disease, independent of all other risk factors (Morris *et al* 1966, Truett *et al* 1967) Other investigations suggest that smoking is related not only to ischaemic heart disease but also to "stroke" (Dawber and Thomas 1969) and to occlusive disease of the arteries of the leg (Widmer *et al.* 1969 Räf 1969 Kjeldsen 1970).

It seems safe to say that a manifest relation exists between smoking and arteriosclerotic disease in different parts of the arterial tree

The statistical correlation between smoking and flow capacity has been mentioned in the previous chapter This chapter presents a more detailed analysis of various smoking habits and their relation to the magnitude of the flow capacity

RESULTS

The reliability of the questionnaire as regards smoking habits proved satisfactory (see chapter 3). Table 20 presents the smoking habits of the total material. Thirty-seven per cent smoked

Table 20 Smoking habits of the subjects (n = 703)

				Smokers									
								Total tobacco consumption gm/day					
Never smoked		Ex-smokers		Non-inhalers		Inhalers		1–14		15–24		>25	
n	%		%	n	%			n	%	n	%	n	%
108	(15)	159	(23)	77	(11)	359	(51)	258	(37)	141	(20)	37	(5)

8. CALF BLOOD FLOW AND PERIPHERAL RESISTANCE AT DIFFERENT LEVELS OF BLOOD PRESSURE

The magnitude of the arterial blood pressure is determined primarily by two factors, the cardiac output (systemic blood flow) and the resistance to blood flow (total peripheral resistance).

The common opinion held earlier was that the primary disturbance in essential hypertension is an increased peripheral resistance (Werkö and Lagerlöf 1949, Varnauskas 1955, Freis 1960, Horrobin 1966). In recent years, however, there have been indications that a large number of patients with early hypertension of the essential type are characterized by an increased cardiac output at rest and normal peripheral resistance. This has been termed *hyperkinetic circulation* (Bello *et al.* 1965, Finkielman *et al.* 1965, Lund-Johansen 1967, Sannerstedt 1969).

Some investigators state that hypertension with increased peripheral resistance can be explained by a pressure-induced adaptive morphological change in the resistance vessels, whereas the vasomotor tonus remains within normal limits (Folkow *et al.* 1958, Conway 1960, Sivertsson 1970).

This alteration of the resistance vessels has not been classified as arteriosclerosis but is considered to be a hypertrophy of the arterial walls.

The report in this chapter consists of primary data gathered in connection with the population study. A more complete account of a therapeutically planned 1-year study comprising specific members of the population will be presented later in separate articles.

The purpose of this chapter is to elucidate the following problems:

(1) Is high blood pressure in 55-year-old males associated with hyperkinetic circulation?

(2) What circulatory changes can be seen in subjects undergoing treatment for hypertension?

(3) How can the peripheral resistance to blood flow in the calf at rest and during reactive hyperaemia at various levels of systolic and diastolic blood pressure be characterized?

Special methodology

In order to estimate the importance of the level of blood pressure in the studied population, a special group-assignment has been arranged as follows (Figure 8):

I. *≥165/≥110*. This group is composed of subjects with systolic blood pressure of ≥165 mm Hg and a simultaneous diastolic blood pressure of ≥110 mm Hg. None received treatment for hypertension at the time of the study. This group is comprised of 5% of the material (n=34).

II. *Systolic hypertension.* This group is comprised of the 5% of the material with the highest systolic blood pressure (n=34).

III. *Diastolic hypertension.* The 5% with the highest diastolic blood pressure are found here (n=34).

IV. *Systolic hypotension.* The 5% of the material with the lowest systolic blood pressure were assigned to this group (n=34).

V. *Diastolic hypotension.* The 5% with the

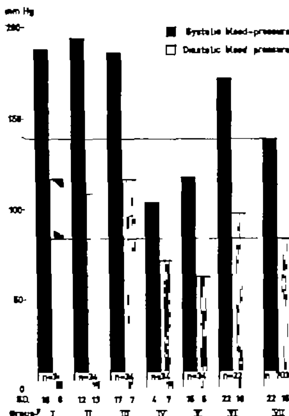


Fig 8 Resting mean arterial blood pressure in the blood pressure groups.
Group structure described on page 50 – 51

lowest diastolic blood pressure are in this group (n = 34)

VI. *Treated* This group includes individuals subjected to more or less active blood pressure treatment. Subjects taking digitalis were excluded (n = 22)

VII. *The total material* (n = 703). Of these, 684 had been examined with plethysmography

Overlapping occurred between some groups. Between group I and VI there was no overlapping. Group III is essentially identical with group I except for 4 subjects. Twenty-one of the 34 subjects in group II are also included in group I Ten subjects belong to both group IV and V

Blood pressure treatment was not given to any subject in group I IV and V Treatment was given to 4 subjects in group II and to two subjects in group III

The casual sitting blood pressure was determined as previously described. The heart rate at rest was determined with ECG

As the material was grouped on the basis of blood pressure, the flow capacity has not been reported, the influence of the blood pressure on the flow being eliminated in the calculation of the predicted flow (see chapter 4). The peripheral resistance has been calculated instead, based on the arm blood pressure measured at plethysmography blood flow at rest, and reactive blood flow of the calf

The quotient between the mean blood pressure of the arm and the calf blood flow has been reported in *Arbitrary Units* in the same way as described by other authors (Folkow *et al* 1958, Conway 1960 Sivertsson 1970).

Statistical comparisons have been made between single groups and the total material throughout.

RESULTS

Height and weight

Anthropometric data are presented in Table 24 All groups with high blood pressure had somewhat higher mean weight than that of the total material ($p < 0.05$) The group with *diastolic hypotension* weighed significantly less ($p < 0.001$). The height was essentially the same in all groups, except the group *systolic hypotension* where the subjects were somewhat taller ($p < 0.05$). Greater weight than, but about the same height as, other groups characterized the hypertension groups.

Heart rate at rest

The heart rate at rest is reported in Figure 9 All groups with high blood pressure had higher mean resting heart rate than did the total material. This rise was most pronounced in the *diastolic hypertension* group ($p < 0.001$).

The hypotensive groups had somewhat lower mean heart rate at rest than did the total material.

Table 24 Anthropometric data of different blood pressure groups.

Group		I	II	III	IV	V	VI	VII
		≥165/≥110	Systolic hypertension	Diastolic hypertension	Systolic hypotension	Diastolic hypotension	Treated	Total material
n		34	34	34	34	34	22	703
Height	m	174	174	174	177	174.5	174	175
	SD	8	8	7	6	7	6	7
Weight	m	79	79	79	72	69	79	75
	SD	13	13	12	12	10	13	11

=0.01 < p < 0.05 = p < 0.001 compared with the total material.

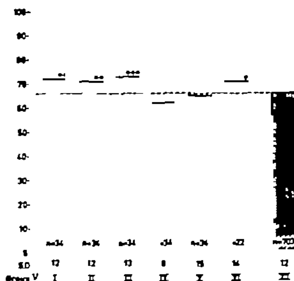


Fig 9 Heart rate at rest in the blood pressure groups. Group structure described on page 50 – 51
=0.01 < p < 0.05 =0.001 < p < 0.01 = p < 0.001 compared with the total material.

Flow resistance at rest

The flow resistance at rest, *i.e.* the quotient of mean blood pressure at plethysmography and calf blood flow at rest, is presented in Figure 11. The mean rest flow resistance was increased in all hypertension groups, except the treated group,. Most of these latter subjects were treated with thiazides.

Reactive calf blood flow

The reactive calf blood flow is presented in Figure 12. Both first flow and peak flow after



Fig 10 Rest flow in the calf according to blood pressure groups.
Group structure described on page 50 – 51
=0.01 < p < 0.05 =0.001 < p < 0.01 = p 0.001 compared with the total material.

Calf blood flow at rest

Calf blood flow at rest, or rest flow is presented in Figure 10. The mean rest flow was significantly higher in all hypertension groups, except the group *diast hypertension*, where the mean rise was mo t. With *systolic hypotension* there was a sig ntly reduced mean rest flow whereas the g *lastolic hypotension* had a rest flow abo o the mean of the total material. The h n blood flow at rest was observed *in t l group*

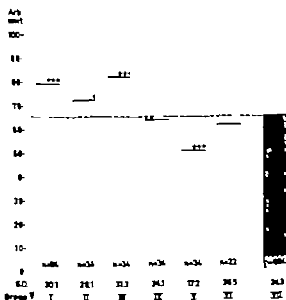


Fig 11 Resistance to blood flow at rest in the calf according to blood pressure groups.
Group structure described on page 50 – 51
–0 01 < p < 0 05, –0 001 < p < 0.01 –p < 0.001
compared with the total material

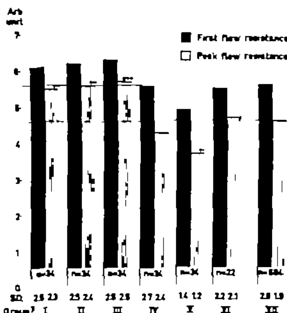


Fig 13 Resistance to first and peak flow in the calf according to blood pressure groups
Group structure is described on page 50 – 51
–0.01 < p < 0.05, –0.001 < p < 0.01 –p < 0.001
compared with the total material

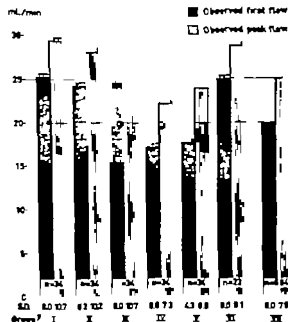


Fig 12 Observed first and peak flow in the calf according to blood pressure groups.
Group structure is described on page 50 – 51
–0 01 < p < 0.05, –0.001 < p < 0.01 –p < 0.001
compared with the total material.

3 minutes of arterial occlusion varied with the level of the blood pressure. The mean first flow was significantly elevated in all the hypertension groups, significantly lower in *systolic hypotension*, and moderately decreased in the *diastolic hypotension* group. The peak flow behaved as the first flow although the differences were not quite so pronounced.

Reactive flow resistance

Reactive flow resistance, *i.e.* the quotient of mean blood pressure at plethysmography and first flow and peak flow after 3 minutes of arterial occlusion, is reported in Figure 13

Mean first flow resistance was moderately increased in the hypertension groups, but not significantly so There was a significantly increased peak flow resistance in all the hyper tension groups, except the treated group where no increase in resistance was observed.

DISCUSSION

The previous opinion that a primary disturbance in essential hypertension is an increase of the peripheral resistance has recently had to give way to the now clear fact that in many cases there is a normal peripheral resistance but elevated cardiac output. Such a hyperkinetic circulation has primarily been considered characteristic of labile hypertension (Finkielman *et al* 1965 Frohlich *et al* 1969) However in Sannerstedt s material (1969), hyperkinetic circulation was seen in early uncomplicated hypertension with the influence of age, sex, and physique statistically accounted for In well-established essential hypertension and in hypertension of non-essential nature, however it seems clear that there is in most cases an increase of the peripheral resistance while the cardiac output is usually normal or in advanced cases even reduced (Pickering 1968 Frohlich *et al* 1969 Sannerstedt 1970).

Hyperkinetic circulation has been considered to exist mainly in young hypertensive individuals, whereas hypertensives over the age of 50 would show a normal or reduced cardiac output and an increased peripheral resistance (Lund-Johansen 1967). Investigations carried out by Amery *et al* (1967) seem to indicate that exercise induced cardiac output decreases as age increases. According to Strandell (1964) a decrease of cardiac output with increasing age should be present also at rest. Theoretically the cardiac output would decrease with increasing age and with hypertension thus, we could expect an especially manifest reduction of cardiac output in older subjects with hypertension.

In other investigations, a control group comparable to the hypertensive subjects has not general [illegible] been used. In the present study the influence [illegible]f both age and sex has been eliminated as [illegible]ll [illegible]articipants were men and, at the time of the [illegible]stigation, were of the same approximate age [illegible]nfluence of their physique was not elimin[illegible] [illegible]efore group-assignment. The group-assign[illegible] has been made only on the basis of arbitrarily selected "cut-off points" in order to obtain sufficiently large groups with similar blood pressure characteristics. The advantage of this procedure is that it is legitimate to use the mean of the total material as a "normal" value. In the case of the group-assignment used, only constitutional factors could be reasonably expected to influence the obtained results. Furthermore, it was found that the weight in the different groups varied but the height was essentially the same. The plausible explanation for this is that the subjects in the hypertension groups were obese The problem of differences between directly and indirectly measured blood pressure has been thoroughly discussed and although opinions may still differ neither of the methods seems to be markedly influenced by an increased amount of body fat (for literature, see Tibblin 1967). The relation between obesity and blood pressure could thereby appear to be a result of a genuine influence of obesity on blood pressure and not merely of errors of measurement evolving from larger arm circumferences (Tibblin 1967). Therefore *the influence of weight on blood pressure* has not been eliminated at the calculations.

A comparison of single groups with the total material showed a higher mean heart rate in all groups comprised of subjects with hypertension, not excluding individual deviations. Several authors have shown that higher heart rate is the most constant finding in hyperkinetic circulation with hypertension (Widimsky *et al* 1958 Sannerstedt 1966, Lund Johansen 1967 Sannerstedt 1969), whereas the stroke volume is normal. The results from the present study indicate that 55-year-old men with hypertension probably *had hyperkinetic circulation.* Both higher heart rate and higher calf circulation support hyperkinetic circulation in the hypertension groups. This increased circulation could be a regional phenomenon Investigations by Brod *et al* (1962) indicate that the blood flow of the skeletal muscle is increased where there is hypertension, whereas Pickering (1936) failed to find any such increase.

The results of this study therefore indicate the existence of hyperkinetic circulation with hypertension at a relatively advanced age. These characteristics are obviously not restricted to the young hypertension patients as was postulated by Lund Johansen (1967) This author established a low minute volume in hypertensive men above 55 years of age, which might be because no comparison was made with age matched controls.

Hyperkinetic circulation in the hypertension groups was associated with an increased rest flow resistance. This was evident in all the hypertension groups, except that composed of treated patients. This elevated mean rest flow resistance is not necessarily due to a relatively small peripheral vascular cross-section at rest, but might, instead, represent an inability for hypertensive subjects to sufficiently dilate their vascular beds. This would elevate the quotient of mean blood pressure and rest flow which, by definition, produces an increased peripheral resistance (Sannerstedt 1969) The fact that the treated group did not show an elevated rest flow resistance suggests that despite the effects of the disease, the peripheral vascular bed in hypertensive patients will respond favourably to vasodilating stimuli.

The flows and flow resistances during reactive hyperaemia partly illustrate the response of the peripheral vascular bed to a relatively strong vasodilating stimulus. The increase in the flow during reactive hyperaemia was approximately the same among the various groups. The reaction of the vascular bed in the groups with low and high pressure was similar Furthermore, it was noted that the flow resistance during maximum dilation, *i.e* the peak flow resistance, was raised in the hypertension groups in a manner analogous to that of the rest flow resistance. The quotient of rest flow resistance and peak flow resistance was essentially the same in the various groups. This indicates the existence of a condition that could not be overcome by the dilating effect of 3 minutes of arterial occlusion. Underlying mechanisms might be the unsatisfactory effect of the occlusion and/or morphological arterial changes, which in turn could be the effects of adaptive alterations, as described by several other authors (Folkow *et al* 1958 Conway 1963 Sivertsson 1970).

The stability of hypertension in the hypertension group is a pertinent question for future discussion. But it should be mentioned that the group with systolic blood pressure of ≥165 mm Hg and diastolic blood pressure of ≥110 mm Hg, and also a randomly selected control group of the same number were examined regularly for blood pressure during the course of a year It was observed that the blood pressure was surprisingly constant at repeated measurements before the initiation of treatment.

SUMMARY

In untreated hypertensive 55-year-old men, the circulation was found to be hyperkinetic The resting heart rate and the calf blood flow at rest were significantly higher in hypertensive groups than in hypotensive groups. The peripheral resistance to blood flow in the calf at rest was elevated in hypertensive groups, suggesting that the increased rest flow was not compensated for by a physiological dilation of the peripheral vascular bed. This is thought to be due to morphological arterial changes, because a raised resistance was also observed during vasodilation

Subjects undergoing treatment for high blood pressure had an elevated calf blood flow at rest and an increased heart rate. The treatment had evidently caused a peripheral vasodilation but the heart rate was still high. Treatment of hypertension does not appear to have affected the hyperkinetic component.

SUMMARY

Venous occlusion plethysmography was used to measure the arterial calf blood flow in a defined population of 55-year old men. The objectives were:

(1) to evaluate the utility of venous occlusion plethysmography as a method of epidemiologic investigation

(2) to validate the diagnosis of intermittent claudication established with a cardiovascular questionnaire recommended by WHO

(3) to compare the results of venous occlusion plethysmography with other data gathered in connection with the population study (medical history clinical findings, laboratory data).

Full participation was obtained from 703 (87 %) of 809 randomly selected men born in 1914 and residing in Malmö, Sweden, at the time of the study

Limited participation by 64 of 106 men who did not appear at the examinations was obtained by home visits, telephone interviews, letter questionnaires, and hospital dossiers.

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Significant negative correlation was demonstrated between first flow and standing height.

The influence of blood pressures, pulse rate, and standing height on the first flow was mathematically accounted for and for every subject, an index was calculated. This index $\left(\frac{\text{observed first flow}}{\text{predicted first flow}} \times 100\right)$ has been called *flow capacity* in this report. Group assignment has been based on flow capacity

The flow capacity is considered an adequate measure of the reserve function of the arteries in the legs, thereby indirectly reflecting the possible existence of arterial disease.

According to the WHO questionnaire, intermittent claudication was present in 20 subjects (2.8 %). Arterial flow insufficiency could be demonstrated in only 6 of these subjects at a more thorough examination.

On the basis of plethysmographic findings, occlusion or near occluding stenosis in the iliofemoral arteries was judged to exist in 8 subjects (1.1 %). The diagnosis was verified angiographically in 7 subjects, and in one subject at autopsy Five of these 8 subjects had intermittent claudication according to the questionnaire: three had not, because of concurrent diseases which limited their ability to walk.

Four of the 8 subjects with obliterating iliofemoral artery disease had suffered at least one myocardial infarction, two of these four had

also suffered cerebrovascular disease (stroke).

Hypertriglyceridaemia, hypercholesterolaemia, lipoprotein abnormalities, and systolic hyper tension were clearly related to occlusive disease in the iliofemoral arteries no correlation was demonstrated between these variables and the magnitude of the flow capacity in the absence of occlusion.

High arterial flow capacity in the legs was related to high, regular spare-time physical activity High, regular spare-time physical activity was significantly more common among ex-smokers than among smokers.

The flow capacity in the legs was reduced in direct proportion to tobacco consumption per day this was true regardless of the mode of smoking.

In groups with high blood pressure, the circulation was found to be hyperkinetic, heart rate at rest and calf blood flow at rest being significantly higher than in the total material.

The peripheral resistance to blood flow in the calf at rest was elevated in groups with high blood pressure, suggesting that the increased rest flow was not compensated for by a physiological dilation of the peripheral vascular bed. This is thought to be due to morphological arterial changes, as an increased resistance was observed also during vasodilation (reactive hyperaemia).

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Carlson, L. A., Allmänna synpunkter på behandling vid hyperlipidemier Läk. Tidn. 67 33, suppl IV 1970

Carlson, L. A. and Wahlberg, F Serum lipids, intravenous glucose tolerance and their interrelation studied in ischaemic cardiovascular disease. Acta med. scand. 180: 307 1966.

Carlson, L. A. and Lindstedt, S., The Stockholm prospective study I The initial values for plasma lipids. Acta med. scand suppl 493 1968.

Conway J The nature of the increased peripheral resistance in hypertension. Amer J Cardiol 5 649 1960

Conway J., A vascular abnormality in hypertension. A study of blood flow in the forearm. Circulation 27 520, 1963

Cooper G R., Milbank mem. Fd Quart. 43 (Part 2) 49 1965.

Dahn, I., On clinical use of venous occlusion plethysmography of calf I. Methods and controls. Acta chir scand. 130- 42, 1965

Dahn, I On clinical use of venous occlusion plethysmography of calf. II Results in patients with arterial disease. Acta chir scand 130- 61 1965

Dalderup, L. M., Zwartz, J A., Keller G H. M., Schouten, F and van Haard, W B., Serum lipids, typing, fibrinolysis, and smoking. Brit med. J 1 223 1970

Dawber T R., Meadors, G F and Moore, Jr F E., Epidemiological approaches to heart disease: Framingham study Amer J publ Hlth 41 279 1951

Dawber T R. and Thomas, H E., Die Epidemiologie des Schlaganfalls. Dtsch. med. J 20- 33, 1969

Documenta Geigy Scientific tables. J R Geigy S A Basle, 1962.

Duguid, J B. and Robertson, W B. Effects of atherosclerosis on coronary circulation. Lancet 1 525, 1955

Eckstein, R. W Effect of exercise and coronary artery narrowing on coronary collateral circulation Circulat. Res. 5 230, 1957

Epstein, F H An epidemiological study in total community- the Tecumseh project Univ Mich med. Bull, 26 307 1960

Epstein, F H., The epidemiology of coronary heart disease. A review J chron. Dis. 18 735, 1965

Erdweg, H and Maurer H J Peripherie arterielle Verschlusskrankheit und Koronarveränderungen im EKG Bruns Beitr klin. Chir 217 703, 1969

Ericson, B., Haeger K and Lindell, S. E., Maximal flow capacity before and after training. I "Coronary Heart Disease and Physical Fitness Ed. Andrée Larsen, O and Malmborg, R. O Munksgaard, Copenhagen, 1971

Faigel A., Haeger K., Lindell, S.-E. and Olsson, N M., Arteriography plethysmography and walking test in arterial oolliteration of the legs. Vasc. Dis. 4 280, 1967

Finkielman, S Worcel, M and Agrest, A. Hemodynamic patterns in essential hypertension Circulation 31 356, 1965

Fitzgerald, D E., Keates, J S. and MacMillan, D Angiographic and plethysmographic assessment of graduated physical exercise in the treatment of chronic occlusive arterial disease of the leg. Angiology 22/2. 99 1971

Fletcher C. M and Horn, D Smoking and health. WHO Chron. 24 345 1970.

Fodor J Hejl, Z., Santrucek, M Vavrik, M Vrbova D and Weber K., The prevalence of ischaemic heart disease and obliterative therosclerosis of peripheral arteries in 60—64 year old males of city population. Cor et vasa (Praha) 10 (1) 41 1968

Folkow B., Grimby G and Thulesius, O., Adaptive structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance Acta physiol. scand. 44 255, 1958

Forssman, O and Lindegård, B. The post coronary patient. J psychosom. Res. 3 89 1958

Fredrickson, D S., Levy R. I and Lees, R. S., Fat transport in lipoproteins—an integrated approach to mechanisms and disorders. New Engl J Med 276 34, 94 148, 215 273, 1967

Freis, E. D Hemodynamics of hypertension. Physiol Rev 40- 27 1960.

Frohlich, E. D Tarazi, R. C. and Dustan, H. P Reexamination of the hemodynamics of hypertension. Amer J med. Sci 257 9 1969

Furberg, C. and Dahlén, G Angina pectoris and electrophoresis of lipoproteins. Lecture at "The III Scandinavian Congress of Cardiology" Helsinki, 1971

Furberg, C., Lundkvist, L. and Svärdsudd, K., Preventiv kardiologisk verksamhet i Norrbotten Läk. Tidn. 69- 143, 1972.

Golding, D N Polyarteritis presenting with leg pains. Brit. med. J 1 277 1970.

Goldsmith, J. R. and Landaw S A Carbon monoxide and human health. Science 162: 1352, 1968

Graf K. and Ström, G Grosse und Verhalten der peripheren Durchblutung des Menschen bei vasoregulatorischer Asthenie. Verh dtsch Ges. Kreisl. Forsch. 25 223 1959

Greenfield, A. D Venous occlusion plethysmography Meth. med. Res. 8 293, 1960

Greenhalgh, R. M., Rosengarten, D S., Mervart, I., Lewis, B., Calnan, J S. and Martin, P Serum lipids and lipoproteins in peripheral vascular disease. Lancet II 947 1971

Varnauskas, E., Studies in hypertensive cardiovascular disease with special reference to cardiac function. Scand. J clin. Lab. Invest. 7 1 1955.

Wahlund, H., Determination of the physical working capacity A physiological and clinical study with special reference to standardization of cardio-pulmonary functional tests. Acta med scand. suppl. 215 1948.

Werkö, L., Varför preventiv kardiologi? Läk. Tidn. 66. 5229 1969

Werkö, L. and Lagerlöf H., Studies on the circulation in man. IV Cardiac output and blood pressure in the right auricle, right ventricle and pulmonary artery in patients with hypertensive cardiovascular disease. Acta med. scand. 133 427 1949

Westlund, K. and Nicolaysen, R., Serum cholesterol and risk of mortality and morbidity A 3-year follow-up of 6886 men. Scand. J clin. Lab. Invest 18 suppl. 87 1 1966.

WHO Chron. 19· 354 1965

WHO Chron. 19· 477 1965

Widimsky J., Fejfarova, H. M., Fejfar Z., Dejdar R., Exnerova, M and Pirk, F., Der jugendliche Hochdruck. Arch. Kreisl. Forsch. 28 100, 1958.

Widmer L. K., Morbidität an Gliedmassenarterienverschluss bei 6400 Berufstätigen. Basler Studie. Bibl. cardiol. 13 67 1963. S. Karger Verlag, Basel–New York.

Widmer L. K., Cikes, M Kolb, P., Lundin, H., Elke, M. and Schmitt, H E., Zur Häufigkeit des Gliedmassenarterienverschlusses bei 1864 berufstätigen Männern. Basler Studie II. Schweiz. med. Wschr 97 102, 1967

Widmer L. K., Hartmann, G Duchosal, F and Plechl, S.-Ch., Risikofaktoren und Gliedmassenarterienverschluss. Dtsch. med. Wschr 94 1107 1969

Widmer L. K. and Glaus, L., In Epidemiologie kardiovaskulärer Krankheiten (Hrsg. von Waibel, P und Widmer L. K.) Verlag Hans Huber Bern-Stuttgart–Wien, 1970.

Wilhelmsen, L., The myocardial infarction clinic in Göteborg–organization and preliminary results. Pehr Dubb Journalen 4 1969

Wilhelmsen, L. and Tibblin, G., Physical inactivity and risk of myocardial infarction.–The men born in 1913 study In "Coronary Heart Disease and Physical Fitness Ed Andrée Larsen, O and Malmborg, R. O Munksgaard, Copenhagen, 1971

Wilhelmsen, L., Tibblin, G Fodor J and Werkö, L., A multifactorial primary preventive trial in Gothenburg, Sweden. In "Coronary Heart Disease and Physical Fitness Ed. Andrée Larsen, O and Malmborg, R. O Munksgaard, Copenhagen, 1971

Wilkins, R. W and Eichna, L. W., Blood flow to the forearm and calf effect of changes in arterial pressure on blood flow to limbs under controlled vasodilatation in normal and hypertensive subjects. Bull. Johns Hopk Hosp. 68 477 1941

Wollenweber J., Doenecke, P., Greten, H., Hild, R., Nobbe, F., Schmidt, F H and Wagner E., Zur Häufigkeit von Hyperlipidämie, Hyperurikämie, Diabetes Mellitus, Hypertonie und Übergewicht bei arterieller Verschlusskrankheit. Dtsch. med. Wschr 96 103, 1971

World Health Organization. Working group on ischaemic heart disease registers. Euro 5010 (1–4). Copenhagen, 1969 1970.

World Health Organization. Control of stroke and hypertension in the community Report of a WHO meeting. CVD 71 3 Geneva, 1971

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Clinical Haemodynamic and Angiocardiographic Evaluation

By Ebba Enghoff

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Clinical, Haemodynamic and Angiocardiographic Evaluation

By

Ebba Enghoff

Translated by Maud Marsden

Uppsala 1972
Almqvist & Wiksells Boktryckeri AB

CONTENTS

ABBREVIATIONS

AI	Aortic incompetence
Ao	Aorta
AS	Aortic stenosis
A V	Atrio-ventricular
AVD_{O_2}	Arterio-venous oxygen difference
BSA	Body surface area
CI	Cardiac index
CO	Cardiac output
D	Diastole
ECG	Electrocardiogram
EDV	End-diastolic volume
ES	Extrasystole
ESV	End-systolic volume
$FEV_{1.0}$	Forced expiratory volume in one second
FVC	Forced vital capacity
HR	Heart rate
Kpm	Kilopondmeter (100 kpm/min. = 16.34 Watt)
LA	Left atrium
LV	Left ventricle
LV_{ED}	Left ventricular end-diastolic pressure
LVH	Left ventricular hypertrophy
MI	Mitral incompetence
MS	Mitral stenosis
MVV_{40}	Max. voluntary ventilation with a fixed respiratory frequency of 40/min
MVV_F	Max. voluntary ventilation with free respiratory frequency
PA	Pulmonary artery
PCG	Phonocardiogram
PCV	Pulmonary capillary venous pressure
Q	Cardiac output
Q_f	Forward effective flow
Q	Regurgitant flow
RA	Right atrium
S	Systole
SV_f	Forward stroke volume
SV	Total stroke volume
TLC	Total lung capacity
VAT	Ventricular activation time
VC	Vital capacity
V_{O_2}	Oxygen uptake
W	Work

Statistical symbols

n	Number of patients
M	Mean
S.D	Standard deviation
S.E.M.	*Standard error of the mean*
S.D	Residual standard deviation
C.L.	Confidence limits
d	Difference
r	Coefficient of correlation
P	Probability

INTRODUCTION

The valvular lesions of aortic incompetence were first described in 1705 by Cowper (cf Major 1945) and in 1832 Corrigan gave a detailed description of the clinical and pathologico-anatomical findings in this disease. From this time it has been possible to diagnose aortic incompetence clinically The improved possibilities of successful surgical correction of this valvular lesion in recent years, however ha e increased the demands for a diagnosis with as exact an assessment as possible of the degree of severity of the incompetence and of the haemodynamic significance of the regurgitation.

The *aim of this investigation* was to attempt, with the aid of clinical, haemodynamic and angiocardiographic findings, to obtain a comprehensive preoperative evaluation of the degree of severity of aortic incompetence in adult patients who during a 5-year period had been referred to this hospital for investigation and preoperative evaluation. The patients were therefore examined with respect to subjective symptoms, physical signs, functional capacity physical work capacity changes in the electrocardiogram at rest and during exercise, lung function, total heart volume and left ventricular volumes, and the findings made were related to the grades of aortic incompetence *as established at thoracic aortography*

The haemodynamic findings at rest, during exercise and under the influence of a drug, amyl nitrite, were studied.

An attempt was made to grade the aortic incompetence objectively by three different methods: (1) calculation of the total diastolic left ventricular filling time by means of thoracic aortography (2) quantitative determination of the regurgitant volume by a combined angiocardiographic and dye dilution technique, and (3) quantitative determination of the regurgitant volume by continuous dye infusion using the upstream sampling technique.

A comparison was made between the regurgitant volume at rest and during exercise.

Further an attempt was made to evaluate roughly the myocardial function of the left ventricle from different observed parameters.

During a 5-year period extending from March 1965 to May 1970, 81 adult patients with aortic incompetence were examined and assessed from clinical, haemodynamic and angiographic aspects. In 76 patients there was isolated incompetence of the aortic valves, while in the remaining 5 patients the aortic disease was combined with mitral incompetence of a mild to moderate degree, which in these cases was considered to be secondary. One further patient, who did not form part of the main series, was included only for one special study. The haemodynamic and angiographic data obtained from the 5 patients with mitral incompetence are reported separately from those of the other patients. This also applies in part to 3 other patients who differed from the rest in that their circulation was affected to a considerable degree by factors other than valvular incompetence alone, namely in one patient (No. 100) by a left-sided pneumonectomy, in the second patient (No. 85) by an implanted fixed-rate transvenous cardiac pacemaker and in the third patient (No 21) by sideropenic anaemia.

Classification of patients

From the findings at thoracic aortography the patients were classified into aortic incompetence grades I–IV according to the magnitude of the regurgitation (see chapter VII). Thirty of the patients with incompetence grade IV were further classified, after calculation of the total diastolic filling time for the left ventricle, into the subgroups $AI_{IV\,n}$ (13 patients) and $AI_{IV<n}$ (17 patients). Table 1 shows the distribution of the patients into the four grades of aortic incompetence with respect to age and sex. The uneven distribution among the four main groups, with so few mild cases, may be attributed largely to the fact that the majority of the patients investigated had been referred for evaluation with respect to operation and thus had a more advanced stage of the disease.

Furthermore the mild cases with no subjective symptoms are often more easily overlooked and re therefore less often referred for examination.

Age and sex

The patients were divided into 2 groups according to their age at the time of the cardiac investigation, below and above 45 years. Thirty-nine of the patients (27 men and 12 women) were younger than 45 years and 42 (37 men and 5 women) were 45 years of age or older. The ages in the whole series varied between 18 and 62 years; the mean age was 42.4 years and the median was 45 years. The men had a somewhat higher mean age (43.8 years) than the women (37.2 years).

The series thus comprised 64 men and 17 women; the ratio of men to women was thus 3.8/1, which corresponds well with the ratio of 4.2/1 found by Hall (1961) in 52 patients with aortic incompetence of rheumatic aetiology. This predominance of men is somewhat greater than is found in other clinical series. Thus in two different series, each comprising 100 patients with pure aortic incompetence, Segal et al. (1956) and Loogen et al. (1969) found ratios of men to women of 3/1 and 2.6/1 respectively, while Wood (1956) reported a predominance of men of 2/1, which ratio was also found by Bland and Wheeler (1957) in a study of 87 patients of ages below 21 years. In a previous series (Enghoff 1967) of 93 patients with AI, examined at this hospital during the years 1959–1966, the ratio of men to women was 2.7/1. Common to the different series is a clear male predominance, even though the relative frequency varies somewhat. Rheumatic fever as a diagnosis had to be based in this series on the case history and could not thus be evaluated primarily according to the criteria of Jones (1965).

Cardiac medication

At the time of admission to this hospital 46 of the patients were receiving *digitalis* (39 men and 7 women), of whom 17 were younger than 45 years and 29 were 45 years or older. The majority of these patients (38) had AI grade IV, 6 had AI grade III and 2 AI grade II.

Five patients were taking *quinidine*, 4 of them in combination with digitalis.

Table 1 *Age and sex distribution of the patients with respect to the classification into AI grades I–IV on the basis of thoracic aortography*

M = males, F = females

AI grade	Number of patients <45 years M	<45 years F	>45 years M	>45 years F	Total	Mean age (range) (years)
I		1			1	18
II	2	2	2		6	35.2 (18–50)
III	2	3	9	1	15	46.8 (27–62)
IV	23	6	26	4	59	42.4 (18–62)
Total	27	12	37	5	81	42.4 (18–62)

Fourteen patients were taking *diuretics*. All of them were over 45 years old. Two had AI grade III and the rest AI grade IV. The serum electrolytes, which were determined in all patients, lay within the normal limits of variation (de Verdier and Killander 1971).

Preoperative mortality

Four of the patients in the series died before undergoing operation. In 3 of them autopsy was performed. For one of the patients (No. 11) it had been decided to wait as regards operation and he was given regular follow-up examinations; he died just under 4 years after investigation at this hospital of subacute bacterial endocarditis. The second patient (No. 84) who had pronounced aortic incompetence combined with mitral incompetence which was probably secondary to left ventricular dilatation was admitted 4 months after the investigation at this hospital in a severely decompensated state and died of multiple pulmonary emboli. The third patient (No. 98) died 2 months after discharge from this hospital, of a dissecting aortic aneurysm due to medial necrosis of the aorta. The fourth patient (No. 79) in whom the cardiac investigation revealed no findings necessitating operation, died at home 3 years after the investigation at this hospital without any direct cause of death being established (he lived under extremely difficult social conditions).

Decision concerning operation

Of the patients in the present series, a total of 31 (25 men and 6 women) all with advanced aortic incompetence underwent operation up to July 1971. In the great majority of cases it was considered at the cardiac investigation at this hospital that on the basis of the clinical haemodynamic and angiographic findings there were clear indications for a relatively early operation. In 3 patients there was a period of expectation of 1½, 4 and 5 years, respectively, from the time of the cardiac evaluation until surgical correction became indicated owing to aggravation of the subjective heart symptoms and an increasing heart size.

A further 5 patients were advised to have an operation but declined as they considered that their disablement due to the cardiac disorder was not of such a degree as to justify the risk involved in surgical treatment.

In 5 other patients with considerable cardiac enlargement and signs of left ventricular failure—both in their case histories and haemodynamically—it was considered, in consultation with the thoracic surgeons, that the risk of an operation was much too great for this to be advised. Furthermore, the mean age of these patients was high, 59.0 years (range 57–62 years). It may be mentioned, further, that one of these patients (No. 85) had an implanted pacemaker because of complete atrioventricular block and another (No. 100) had a considerably reduced ventilatory capacity following a left-sided pneumonectomy.

During recent years the aetiology of aortic incompetence has changed its clinical pattern. As can be seen in Fig. 1 where the different aetiological factors are presented *rheumatic fever* occurred in 27 patients. This means that its relative frequency was 33% which is considerably lower than in other older clinical series, where values of up to 83% may be found (Segal, Harvey and Hufnagel 1956, among others). These authors point out, however that the large predominance of a rheumatic aetiology in their series is probably due largely to geographical conditions and the case selection. In a later clinical analysis of 122 patients with aortic incompetence, carried out during the period July 1966–June 1967 Stapleton and Harvey (1969) found a lower frequency (54%) of rheumatic aetiology In a review of patients with aortic valve disease examined during the period 1961–1968, including 59 patients with AI, Rotman et al. (1971) reported a frequency of 39% On comparison between the series of patients with AI from this hospital in 1959–1966 mentioned previously and the present series collected in 1965–1970 a reduction from 42% to 33% was found in the number of patients with a rheumatic aetiology which is in agreement with the general experience that rheumatic fever as well as the valvular lesions which it causes, have decreased in frequency successively during the last few decades (Hall 1961 Ekelund et al. 1967 Vendsborg et al. 1968, Sievers and Hall 1971) Storstein (1969) reported as low a frequency figure for rheumatically caused pure aortic incompetence as 1 out of 15 adult patients (7%) investigated during the years 1965 to 1968 In an autopsy series comprising 126 patients with AI from the years 1956–1967 however Baroudess & Sande (1969) found rheumatic heart disease as the aetiological factor in as many as 78%

The age at onset of the first attack of rheumatic fever in the 27 patients (20 men and 7 women) was, on the average 15 years (range 6–29 years). This is in essential agreement with the finding of Hall (1961) and later Sievers and Hall (1971) in rheumatic endocarditis and of Segal et al. (1956) in AI of rheumatic origin. In 5 of the present patients one recurrent attack occurred and in 1 patient 2 recurrences. A mean period of 27 years (range 4–48) had elapsed from the onset of the first attack of rheumatic fever up to the time of investigation at this hospital (Fig. 2). At this time about 3/4 of these patients (74%) had pronounced aortic incompetence of grade IV 5 (19%) grade III and 2 (7%) grade II. No definite relationship between the degree of incompetence and the time interval between the first attack of rheumatic fever and the investigation could be traced.

Of the 2 patients for whom *streptococcal infection* had been noted as the aetiological factor one—a woman—had had scarlet fever at the age of 12 years with subsequent joint symptoms and a cardiac murmur discovered at the same time, and the other—a 19-year-old boy—had a cardiac murmur discovered after an infection at the age of about 9 years, with elevation of the antistreptolysin 0 titre Thus both of these conditions may be regarded as probable rheumatic heart disease, even if the strict criteria of rheumatic fever were not fulfilled.

According to several authors only about half of all patients with so-called *rheumatic heart disease* have a history of diagnosed rheumatic fever (Hall 1961 Friedberg 1966, Elliot 1968 Vendsborg et al. 1968 Burch et al. 1970). In a series covering the period 1953–1964 Vendsborg et al. (1968) found that the frequency of chronic rheumatic valvular disease declined, which they considered was mainly due to the fact that the number of patients with a history of rheumatic *fever decreased, while the group without* known rheumatic fever remained essentially unchanged. The authors suggest that this might be explainable either by a subclinical rheumatic infection or by a misleading classification of valvular disease of non-rheumatic aetiology as rheumatic heart disease. Hall (1961) who in his follow-up studies of rheumatic heart disease found a better prognosis for patients with no history of acute rheumatic

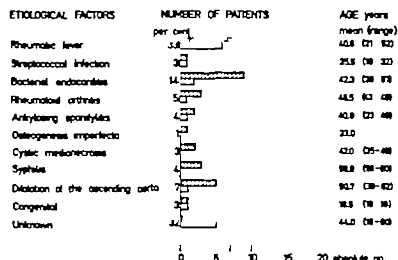


Fig. 1. Age and sex distribution with respect to the different etiological factors. The numbers of patients are given both as absolute figures and as percentages of the total series. Cross-hatched bars = males; unfilled bars = females.

fever also questions whether all patients designated as rheumatic valvulitis really do have one single aetiological factor

On the basis of experimental studies on animals, Burch et al. (1970) discuss the role of *virus* infections in the occurrence of valvular diseases in man. They express the opinion that viruses may play a significant role in the pathogenesis of so-

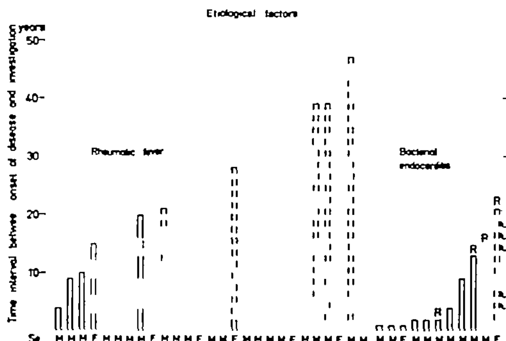


Fig. 2. The patients are ranked according to the time interval in years between the onset of the rheumatic fever and the bacterial endocarditis, respectively and the investigation at this hospital. AI grade II — — AI grade III — — — AI grade IV — — — *M* males, *F* females *R*, rheumatic fever

called rheumatic heart disease in man and that this would explain the rheumatic valvular diseases with no history of acute rheumatic fever. Burch et al. (1966) induced endocarditis in 55% of mice inoculated with Coxsackie virus, with involvement of the aortic valves in 10% of these cases as shown by histological studies. The possibility that virus infections may give valvular lesions has also been suggested by Sainani et al. (1968) who in a series of 22 adults with pericarditis and/or myocarditis caused by Coxsackie B virus found signs of mitral incompetence in 2 patients and combined mitral stenosis and mitral incompetence in 1 patient. In these patients, however, it cannot be decided with certainty whether the mitral incompetence is secondary to the myocardial lesion or due to valvulitis caused by the viral endocarditis.

Bacterial endocarditis has become one of the most common contributory causes of AI (Cleland et al. 1968, Loogen et al. 1969, Storstein 1969, Rotman et al. 1971) and occurs both in normal aortic valves and secondary to known earlier valvular disease (Friedberg et al. 1961, Tompsett 1967, among others). This finding is also reflected in the present series (Figs. 1 and 2), where there was a history of bacterial endocarditis in 11 patients (14%), 4 of them with rheumatic lesions of the valves, 1 with previously diagnosed AI, possibly occurring in association with severe tonsillitis, and 1 with bicuspid valves. In a further 2 patients an unspecified murmur of unknown origin was noted prior to the onset of the bacterial endocarditis. Thus only 3 of these 11 patients (Nos. 40, 104 and 106) had no known previous heart disease. One female patient (No. 17) had 4 attacks of bacterial endocarditis subsequent to 2 attacks of rheumatic fever. The causative bacterial agent in 6 of the 11 patients was streptococcus viridans, in 1 acute case of sepsis beta-haemolytic streptococci, and in another patient staphylococcus aureus. In the other 3 patients, for whom no positive blood culture was obtained (in one of them no blood culture seems to have been performed), the clinical course gave strong reasons to suspect that bacterial endocarditis had occurred.

At operation in 2 of these patients a perforation was found in the non-coronary cusp, as well as in another of the 7 patients with bacterial endocarditis who underwent operation. Also in the patient with bicuspid valves (No. 36) a perforation was found. In case No. 104 with staphylococcus aureus infection only a residual fragment of the left cusp was present. One of the patients (No. 84) who had had rheumatic fever died of cardiac failure years after the onset of the bacterial endocarditis. At autopsy fenestrated aortic valves were found. This is a fairly common anatomical finding which seldom gives rise to valvular regurgitation because most fenestrations are located in the line of closure of the aortic valve (Symbas et al. 1969). On analysis of 47 autopsy cases of bacterial endocarditis, Tompsett and Lubash (1961) observed aortic valve perforation in 15 patients, of whom 10 had developed dynamically significant AI during the course of the endocarditis. The most common site of perforation was the posterior cusp and in 2 of the 10 patients rupture of the valve had also occurred.

The frequencies of the most common endocarditis-inducing bacterial agents are reported in several clinical series to be 39–50% for streptococcus viridans and 15–23% for staphylococci (Blount 1965, Lerner and Weinstein 1966, Tompsett 1967). According to Friedberg et al. (1961) the number of negative blood cultures in bacterial endocarditis generally lies at about 10–20%, which is in relatively good agreement with the frequencies of 23.6% and 14% found by Blount (1965) and Lerner and Weinstein (1966), respectively. Thus the general endocarditis series referred to above correspond relatively well with the findings in the present series of patients with aortic incompetence.

Fig. 2 illustrates clearly the difference in time intervals between the onsets of rheumatic fever and bacterial endocarditis, respectively, and the time of investigation at this hospital. For bacterial endocarditis this mean interval was 6.5 years for the whole group, with a wide range from 1 to 21 years. The 7 patients who had not had rheumatic fever had the shortest time interval, a mean of 2.9 years, while for the 4 patients with rheumatic valvular lesions it was 12.8 years; this may be considered as an expression of the more rapid course when incompetence of the aortic valves occurs suddenly, as is the case in the acute form of endocarditis (Friedberg et al. 1961, Fowler et al. 1967, among others). Twenty-two per cent of the patients with a rheumatic aetiology included in the series with aortic incompetence

of Segal et al. (1956) developed bacterial endocarditis, and 3.6 years later on the average, underwent cardiac evaluation in respect to operability.

In both *rheumatoid arthritis* and *ankylosing spondylitis* aortitis with accompanying dilatation of the aortic valve ring, leading to AI, may be found (Zvaifler and Weintraub 1963 and others). According to Clark et al. (1957) in patients who have had classic rheumatoid arthritis it may be expected that 2% will show rheumatic heart disease with rheumatoid granulomas in the myocardium and within the valve leaflets as a sign of systemic manifestation of the disease: this has been confirmed by several authors in autopsy findings (Baggenstoss and Rosenberg 1941, Lebowitz 1963, Weintraub and Zvaifler 1963, Sokoloff 1964, Roberts et al. 1968).

Clark et al. (1957) have described the aortic lesions in 22 patients with rheumatoid arthritis, all of whom except 2 showed signs of ankylosing spondylitis in addition. The pathologico-anatomical picture in this latter condition was first described as early as in 1936 by Mallory. In several series of patients with ankylosing spondylitis AI has been found to occur in 1–2% (Bernstein and Broch 1949, Davidson et al. 1963 among others), *while other investigators report a higher* figure, about 10% (Storstein and Waaler 1959, Weed et al. 1966). In an autopsy series including 34 patients with pure aortic incompetence the aetiology in 15% was ankylosing spondylitis (Roberts 1970 *b*). A lower frequency figure of 5% was found by Schilder et al. (1956) in 100 patients who had been referred for surgical treatment of AI. This latter figure is in good agreement with the findings in the present series. As can be seen in Fig. 1, one of the patients with this complaint was a woman (No. 111) who also had peripheral joint involvement, and she is also therefore assigned to the group with rheumatoid arthritis.

In addition to ankylosing spondylitis one of the men (No. 48) also had *osteogenesis imperfecta* which is included in the group of diseases which McKusick (1966) has classified as "heritable disorders of connective tissue" and which can be associated with AI (cf. Criscitiello et al. 1965). Also belonging to this group of inherited connective tissue defects is Marfan's syndrome, in which *cystic medionecrosis* of the aorta is included as a manifestation, which, however, not rarely occurs alone without the other characteristic clinical features. This applied to 2 of the patients in the present series. This degeneration of the aortic media can be the result of either a congenital or acquired pathological process, which is often named idiopathic cystic medionecrosis and gives rise to aneurysmal dilatation of the ascending aorta (Bahnson and Nelson 1956, Weaver et al. 1959, Eliot et al. 1964, Cooley et al. 1967, Ferlic et al. 1967, Layman and Wang 1968, Gerbode et al. 1969). Both the patients just mentioned had a thin aneurysmally dilated ascending aorta and AI of grade IV. They both died of dissecting aortic aneurysm. Autopsy revealed changes similar to those in cystic medionecrosis of the aorta. One of the patients (No. 42) died 2 months after operative correction of the valvular disorder, and the other 1½ years after a violent thoracic injury with subsequent subjective cardiac symptoms. The course of the disease in the latter patient resembles a case of post-traumatic AI described by Dimond et al. (1957) occurring in a patient with Marfan's syndrome with no previous cardiac symptoms. Rupture of the aortic valve is the valvular lesion most frequently seen in non-penetrating cardiac injury even in normal valves (Howard 1928, Leonard et al. 1955, Levine et al. 1962, *Najafi et al. 1968*).

The most common causes of aneurysmal dilatation of the aortic root apart from cystic medionecrosis are arteriosclerosis and syphilis with secondary AI (Marquis et al. 1968, Gerbode et al. 1969, Najafi 1971, among others). Of the 6 patients in the present series for whom *dilatation of the ascending aorta* was noted as the aetiological factor underlying the incompetence of the aortic valves, 2 were 62 years old and the aortic incompetence murmur had only been known of for 1 year so that in these cases the cause may conceivably have been senile dilatation (Bedford and Caird 1960, Eliot et al. 1964, Bleich et al. 1966, Eliot and Mork 1967), while in the other 4 patients the cause was not clear (cf. Storstein 1969). In a series of 122 patients with AI, Stapleton and Harvey (1969) found aortic root disease in 9%, which figure is of the same magnitude as in the present series.

It is a general experience that the number of patients with AI caused by *syphilis* has decreased considerably during the last decades (Beerman et al. 1962), and that this aetiology is nowadays

rare (Loogen et al. 1969 Storstein 1969 and others) Previously the frequency of this aetiological factor was reported to be 12–19% (Campbell and Shackle 1932, Segal et al. 1956 Bedford and Caird 1960) In their autopsy series including a total of 258 patients with AI, Barondess and Sande (1969) found that syphilis as an aetiological factor decreased from 15% during the period 1932–1943 to 5% during 1956–1967 In a clinical analysis, during the period July 1966 – June 1967 of 122 patients with AI, Stapleton and Harvey (1969) calculated this frequency to be 2.5% Rotman et al. (1971) reported a frequency of 7% in their review of patients with AI from the years 1961–1968. In the present series it was 4% It can be seen in Fig. 1 that these patients with a syphilitic aetiology had the highest mean age, and the same was found in the series of Campbell and Shackle (1932) and in that of Segal et al. (1956) among others.

Congenital AI occurs mostly together with other cardiovascular malformations and is rare as an isolated disease (Frahm et al. 1961 Beuren 1965 Levine and Harvey 1959) In the great majority of cases the cause of the valvular incompetence is a congenital bicuspid aortic valve. This anomaly has been described in detail by several authors including Koletsky (1941) Edwards (1961) Elliot et al. (1964) Roberts (1970 *a*) and Carter et al. (1971) In different clinical series the frequency of congenital AI has been reported to be 0.3–2.3% (Levine and Harvey 1959 Stapleton and Harvey 1969 among others) the lowest figure has been given by Levine and Harvey who clearly state that a diagnosis of congenital AI can only be made if a murmur is discovered in infancy or early childhood. In my 2 patients, who comprise 3% of the whole series, the murmur was discovered at the age of 7 years without any evidence in their history indicating previous relevant infection, and these valvular lesions can therefore be regarded with a high degree of probability as congenital.

The number of patients with an *unknown aetiology* in the present series corresponded to 32% and was thus almost as large as the number of patients with rheumatic heart disease. On closer analysis of this group 4 patients are found whose disease was diagnosed at the age of 10–16 years without any preceding rheumatic fever or other severe infection and thus in these patients the cause could be congenital. Three of these patients were 18, 21 and 25 years old at the time of investigation at this hospital, while the fourth was 58 years old. This latter patient—the only of the 4 to undergo surgical treatment—was found at operation to have bicuspid valves, which may have been an acquired change. On the other hand, bacterial endocarditis occurs in a high frequency in cases with congenital bicuspid aortic valves (Edwards 1961 Roberts 1970 *a*, Carter et al. 1971) Three patients may be assumed to have had an infectious aetiology namely two patients with recurrent severe tonsillitis during childhood and one patient with a severe protracted upper respiratory infection, which led to absence from school for one year A murmur was discovered in each of these patients in association with the mentioned infections.

In 2 further patients (Nos. 81 and 83) who were 59 and 60 years old and had a history of slight hypertension, a murmur had been discovered less than 1 year before the investigation. In these cases it is conceivable that age-dependent alterations of the aorta may have been combined with the hypertension (Bedford and Caird 1960 Elliot et al. 1964 Bleich et al. 1966 Elliot and Mork 1967 Barondess and Sande 1969) such alterations cause dilatation of the aortic valve ring or degenerative changes of the valves themselves (Sugiura et al. 1969) In one of these 2 patients (No. 81) the diameter of the aortic valve annulus was 49 mm, and in the other (No. 83) only 36 mm. Concerning the other 17 patients with an unknown aetiology it may be mentioned that in 8 of them a murmur was only discovered after the age of 45 years (46–53 years) and at the time of the cardiac investigation it had only been known of for 1–6 years.

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III SUBJECTIVE SYMPTOMS AND FUNCTIONAL DISABILITY IN RELATION TO SOME CLINICAL FINDINGS

METHODS

The patients were hospitalized during the period of the examination which lasted about 1 week. The examination comprised the taking of a case history a general clinical examination and an examination of the physical cardiac state electrocardiography and a graded exercise test, and phonocardiography all of which were performed by the author In addition there were various lung function tests, determination of the basal metabolic rate different blood and urine analyses and chest roentgenography Finally cardiac catheterization and angiocardiography were performed.

Functional classification

On the basis of the case history the patients were divided into function classes according to the classification of the New York Heart Association (1953) as modified by Bishop and Wade (1963) with divison of class III into classes III A and III B

Class I Patients with no disability

Class II Patients whose physical activity is not impaired except when undertaking severe or competitive physical exercise, running, climbing or hea y work

Class III A Patients who suffer slight discomfort in the normal activities of life but are able to walk an English mile or more on the flat at their own peed and can climb stairs slowly without undue discomfort

Class III B P tients who can manage only the lightest of activity w thout discomfort, can walk only short distances on the flat without resting and ha e d fficulty in going upstairs

Class IV Severely disabled patients confined to chair or bed.

Electrocardiogram (ECG)

The ECG was recorded on direct writing four channel apparatus (Mingograf 4 during the first years and Mingograf 34[1] since 1968). Leads I II III aVR, aVL, aVF and the precordial leads V_1 V_2, V_4 V_5 and V_7 were used at rest and leads CH_{2-7} during exercise with the indifferent elec trode attached to the forehead. The paper speed was 50 mm/sec. The ECG was recorded at rest in the supine position before and about ½ min and 4 and 10 min after exercise. An orthostatic test was carried out before the exercise test and the heart rate and ECG were recorded after standing for 8 minutes.

Exercise test

The exercise test was performed in the sitting position on an electrically braked bicycle ergometer (Holmgren and Mattsson 1954) with stepwise increases of the load (Sjöstrand 1947 Wahlund 1948) Each work load period comprised 6 minutes. The ECG was monitored continuously on an oscilloscope and was recorded after 5 min utes at each load. The heart rate was counted at 2, 4 and 6 minutes and in the middle of each work period the respiratory frequency was counted and the blood pressure measured (arm cuff) The initial work load was chosen with respect to the patient s history of physical capacity As a rule the first work load for patients in function classes I and II was 200 kpm/min for women and 300 kpm/min for men. In function classes III A and B the test was started at lower work loads. The exercise test was terminated at a heart rate of about 170 beats/min or earlier in the case of subjective symptoms or objective signs of an abnormal reaction Under the assumption of a linear relationship between heart rate and work load the physical work capacity could be calculated in most cases at one of the heart rates 170 150 or 130 beats min (W_{170}, W_{150} and W_{130}) by interpolation or extrapolation (cf Ström 1967) and is expressed as kpm/min A steady state was considered to exist when the increase in heart

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[1] Elema-Schönander Ltd., Stockholm, S eden.

rate at a given work load was not more than 10 beats from the 2nd to the 6th minute or when the increase in heart rate between the 4th and 6th minutes was not greater than 2 beats per min. Since the physical work capacity varied considerably in this series of patients, and since in some cases it was not possible to extrapolate even to W_{130}, the highest work load performed for 6 minutes ($W_{max\ perf}$) and the corresponding heart rate have been given. If on account of an abnormal subjective or objective reaction, a patient was unable to carry through a commenced work load for 6 minutes, the maximal performed work load was recalculated to refer to 6 minutes (Strandell 1964) according to the following:

$$W_{max\ perf\ recalculated} = W + \frac{t \cdot Wd}{6}$$

where W is the highest work load performed for 6 minutes, t is the number of minutes for which the patient worked at the highest work load and Wd the difference between the highest and next highest (W_d) work load in kpm/min. The highest heart rate reached during the highest work load is designated HR_{max}.

Lung function tests

Dynamic spirometry was performed in all cases, using a light-weight spirometer (Spirocombi, Kifa Ltd Stockholm Sweden) which is a slightly modified version (see Berglund et al. 1963) of that described by Bernstein et al. (1952). The vital capacity (VC) forced expiratory volume in one second ($FEV_{1.0}$) and maximal voluntary ventilation with a fixed respiratory frequency of 40/min (MVV_{40}) or with a free respiratory frequency chosen by the patient (MVV) were measured. By FEV% is meant $FEV_{1.0}$ expressed as percentage of VC or FVC (forced vital capacity) whichever was the largest. For evaluation of the maximal respiratory flow rate a Wright's peak flow meter was used (Wright and McKerrow 1959)

In patients over 45 years of age or for whom dynamic spirometry gave pathological values, the total lung capacity (TLC) and its subdivisions were *determined by the helium dilution method using* a closed spirometer (Spirocombi) All volumes are given at body temperature and ambient pressure, saturated (BTPS). The international nomenclature of lung volumes and tests are used (Gandevia and Hugh-Jones 1957). Normal values for ventilatory capacity and lung volumes are obtained from a normal Swedish material (published by Berg*lund et al. 1963 Birath et al. 1963 and Grimby* and Söderholm 1963)

Heart volume

The heart volume was determined with the patient standing, using the formula of Jonsell (1939) For technical reasons the examination could not be performed with the patient sitting. The relative heart volume is given in ml per m^2 body surface area. All heart volumes were evaluated by the same roentgenologist, Uno Erikson M.D (cf Bergström and Erikson 1971) In just under *half of the patients, heart volume determination* was also performed in the supine posture with a right-angled frontal projection and using Jonsell's formula (Bergström 1969)

SUBJECTIVE SYMPTOMS

It is a well known fact that in the absence of complications many patients with AI can live for many years and in the presumably milder cases can have an apparently unshortened lifetime with no limitations in their normal activities (Bailey and Zimmerman 1959 Hufnagel 1961 Friedberg 1966, Eliot and Mork 1967 among others) Even during the time when the valvular disorder is well compensated the patient can have a number of mild subjective symptoms that do not reduce the functional capacity

The *frequencies* of the *different symptoms* at the time of admission to this hospital, *related* to *AI grades* and *function classes*, are shown in Table 2. As mentioned previously the material is selected, and therefore there will most probably be an underrepresentation of symptom-free patients, in particular but probably also of severely disabled patients. This renders difficult a comparison between the different AI grades in this respect. Since the number of patients with isolated AI grad IV amounted to as many as 2/3 of the whole series, it was considered appropriate to divide these patients into 2 groups according *to age, below and above 45 years. By this division* increased information on the symptomatology should be obtained, since it may be assumed that the symptoms will become intensified with increasing age and a longer duration of the valvular

Table 2. *Distribution of symptoms in 75 patients with isolated AI of varying degrees, 5 patients with predominant AI of grade IV combined with MI of a slight to moderate degree and 1 pneumonectomized patient with AI grade IV and, further the relation of the symptoms to the functional classification*

Symptoms	Isolated, AI grade I	II	III	IV <45 y	IV >45 y	AI grade IV + MI	AI grade IV + Left sided pneumo-nect.	Functional classes I	II	IIIA	IIIB	Total No. of pats. with resp. symptoms Abs.	%
1 Ectopic beats			4	17	14	4		12	11	13	5	41	51
2. Throbbing of the heart		1	3	10	7			5	11	4	1	21	26
3 Pulsation of the peripheral vessels			6	16	7	2	1	5	14	9	4	32	40
4. Paroxysmal tachycardia			3	2	3				6	2		8	10
5 Palpitations on effort			1	6	3	2			7	4	1	12	15
6. Increased fatigability			4	5	11	3			8	7	8	23	28
7 Chest pain													
Atypical	1	1	6	8	6	1		2	12	7	2	23	28
Angina pectoris			1		7	1			1	4	4	9	11
8. Dyspnoea on effort													
Moderate			1	3	6	4	1		3	7	5	15	19
Pronounced			1		3						4	4	5
9 Cough (dry)			2	2	6	2			2	5	5	12	15
10. Left ventricular failure			2	1	4	2	1			4	6	10	12
11 Right ventricular failure					1	1					2	2	2
12. Perspiration				2	4					3	3	6	7
13. Dizziness				8	4		1		7	4	2	13	16
14. Asymptomatic		3		5	2	1		11				11	14
Total number of patients	1	6	15	28	25	5	1	27	27	17	10		

heart disease (Friedberg 1966, and others) Further the frequency of additional coronary heart disease increases with increasing age (cf Chasnoff and Silver 1951 Friedberg 1966)

The following explanations for some of the terms used for symptoms in Table 2 may be motivated

Palpitations on effort strong, rapid heart beats on effort

Dyspnoea on effort (*a*) patients with moderate dyspnoea were forced to rest on account of breathlessness after walking upstairs or up a slope even slowly (*b*) patients with pronounced dyspnoea were not able to walk up a flight of stairs without resting because of breathlessness and became out of breath on walking more than a short distance on the flat

Atypical chest pain. uncharacteristic left-sided chest pain or a diffuse sensation of discomfort even at rest and with no definite correlation to effort.

Angina pectoris this term is used according to the criteria of WHO (1959)

Dizziness this wa not actually rotatory in character but a more vaguely described sensation of giddiness, especially on sudden changes of posture.

Left ventricular failure paroxysmal nocturnal dyspnoea, orthopnoea or pulmonary oedema.

Right ventricular failure swelling of the legs and liver enlargement.

I *Frequency of the symptoms and their relation to the different function classes*

Ectopic beats which are usually manifested at rest after exercise were the most common symptom and occurred in about half of all patients. Next in frequency followed subjective symptoms in the form of intense *pulsations* far out in the peripheral parts of the body on physical effort. *Throbbing of the heart* was another early symptom (Wood 1956 and 1968 Segal et al. 1956, Schölmerisch 1965 Eliot and Mork 1967) This symptom, like the two just mentioned, is not usually associated with reduction of the functional capacity This is reflected in the finding that the above three symptoms were the most common of all symptoms in those patients in function class I who were not completely symptom-free; 10 of

these patients had only one of these symptoms and 6 had two or three. Other common symptoms were atypical chest pain, increased fatigability and dyspnoea on effort. Two of the patients in function group I had *atypical chest pain*. Such attacks of pain occurred 6 times as frequently in function class II as in class III B. This symptom is probably unspecific and poorly correlated to the degree of severity of the disease. The same applies to *increased fatigability* which to some extent is age-dependent. *Dyspnoea on ffort* is reported by several authors to be an early symptom (Segal et al. 1956, Degeorges and Delzant 1966, Loogen et al. 1969 among others) Since the degree of effort is important in this connec tion an attempt was made in this study to grade the dyspnoea on effort as moderate and pronounced. patients with moderate dyspnoea were then found in varying function classes depending on the combination with other function-reducing symptoms, while in all 4 patients with pronounced dyspnoea (Nos. 83 85 99 110) the exercise tolerance was restricted by breathlessness. These 4 patients belonged to function class III B. In 3 of them the case history indicated left ventricular failure with pulmonary oedema in one case. A *dry cough* on effort occurred in patients with moderate to pronounced dyspnoea on effort in association with either acute periods of left ventricular failure or deterioration to a more chronic state with reduced left ventricular func tion. *Excessive perspiration* often at night, was also found in patients with a more advanced stage of the disease, in agreement with the observation of Loogen et al. (1969) among others. This also corresponds with the findings of Harvey et al. (1957) in a study of more than 300 patients with severe AI, in whom profuse sweating often ran parallel with the clinical course of congestive failure In the present series *pulmonary oedema* had occurred in 3 (Nos. 29 42 and 85) of the 10 patients with a history of *left ventricular failure* (Nos 29 42, 67 70 81 83 84 85 99 and 100). of these latter patients 2 had also had right ventricular failure (Nos. 83 and 84)

In contrast to the atypical chest pains, true *angina pectoris* (WHO 1959) occurred only in the fairly severely disabled patients in function class III A or B, with the exception of one patient, 62-year-old man in function class II, who only had this symptom on heavy arm work. Of these patients, 9 altogether (Nos. 20, 24 29 39 42, 65 70, 75 77) 3 had been in left ventricular failure, which combination is not uncommon in pronounced AI (Bernsmeier 1965 Friedberg 1966, Shine et al. 1968) Another of the patients (No. 24) had such severe, frequent attacks of pain, provoked both by mental stress and by physical effort, that he sometimes took as many as 50 nitroglycerin tablets in a day This man, as well as one of the two female patients with angina pectoris (No. 77) also had attacks at night. One further patient (No. 67) who has not been included among the 9 mentioned above, had chest pain of the angina pectoris type only at night in association with attacks of paroxysmal dyspnoea and palpitations, precipitated by nightmares, a combination of symptoms which has also been reported by Harvey et al. (1957). These attacks of pain at night combined with palpitations, flushing, respiratory distress and at times sweating have been described by several authors as a special syndrome in severe isolated AI (Lewis 1931 Chiche et al. 1961 Soullé et al. 1964 Stapleton and Harvey 1969) even in young people below the age of 21 (Bland and Wheeler 1957)

The frequency of angina pectoris in AI reported by different authors varies considerably which is probably due to differences in the composition of the various series of patients especially as regards the degree of severity of the disease and the age distribution. Thus, among patients below 50 years of age with a mean age of about 30 years, Degeorges and Delzant (1966) found a frequency of 6% in cases with mild to moderate AI and 15% in those with pronounced AI, which figures are in relatively good agreement with the fre quency of 11% in the present series A similar frequency (7%) was found in the series of Bedford and Caird (1960) comprising 138 patients 65 years of age or older and also (10%) in the study by Bland and Wheeler (1957) of severe AI with a rheumatic origin in young people. A high frequency of angina pectoris of almost 50% was found by Harvey et al. (1957) among more than 300 patients with advanced AI who were investigated prior to surgical correction. A fre quency of 29% (20% under and 41% over the age of 40 years) was noted by Bernsmeier (1965) among 290 patients, Loogen et al. (1969) noted 25% in moderate to severe incompetence and Björk and Cullhed (1969) reported a figure f

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	Isolated, AI grade					AI grade IV		Functional classes				Total No. of pats. with resp. symptoms	
				IV			+ Left sided pneumo-						
Symptoms	I	II	III	< 45 y	> 45 y	+ MI	nect.	I	II	IIIA	IIIB	Abs.	%
1 Ectopic beats		2	4	17	14	4		12	11	13	5	41	51
2. Throbbing of the heart		1	3	10	7			5	11	4	1	21	26
3. Pulsation of the peripheral vessels			6	16	7	2	1	5	14	9	4	32	40
4 Paroxysmal tachycardia			3	2	3				6	2		8	10
5. Palpitations on effort			1	6	3	2			7	4	1	12	15
6. Increased fatigability			4	5	11	3			8	7	8	23	28
7 Chest pain													
Atypical	1	1	6	8	6	1		2	12	7	2	23	28
Angina pectoris			1		7	1			1	4	4	9	11
8. Dyspnoea on effort													
Moderate			1	3	6	4	1		3	7	5	15	19
Pronounced			1		3						4	4	5
9 Cough (dry)			2	2	6	2			2	5	5	12	15
10. Left ventricular failure			2	1	4	2	1			4	6	10	12
11 Right ventricular failure					1	1					2	2	2
12. Perspiration				2	4					3	3	6	7
13. Dizziness				8	4		1		7	4	2	13	16
14. Asymptomatic		3		5	2	1		11				11	14
Total number of patients	1	6	15	28	25	5	1	27	27	17	10		

heart disease (Friedberg 1966, and others) Further the frequency of additional coronary heart disease increases with increasing age (cf Chasnoff and Silver 1951 Friedberg 1966)

The following explanations for some of the terms used for symptoms in Table 2 may be motivated.

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I. Frequency of the symptoms and their relation to the different function classes

Ectopic beats which are usually manifested at rest after exercise were the most common symptom and occurred in about half of all patients. Next in frequency followed subjective symptoms in the form of intense *pulsations* far out in the peripheral parts of the body on physical effort. *Throbbing of the heart* was another early symptom (Wood 1956 and 1968 Segal et al. 1956, Schölmerich 1965 Elliot and Mork 1967) This symptom, like the two just mentioned, is not usually associated with reduction of the functional capacity This is reflected in the finding that the above three symptoms were the most common of all symptoms in those patients in function class I who were not completely symptom-free 10 of

factory for the coronary vessels to be evaluated with certainty In one of these patients (No. 77) considerable difficulties were encountered at operation in inserting the perfusion cannula through the right coronary ostium, which at autopsy a few days later was found to be narrowed and slit-like. Otherwise only slight atheromatosis in the coronary arteries was found in this patient, as also in patient No. 67 who only had attacks of pain at night. In a further 2 of these 7 patients, who were autopsied, moderate atheromatous changes were found but no appreciable narrowing of the lumen. Thus among the patients with a history of angina pectoris in this series a rough evaluation in 2 cases revealed coronary arterial changes of a mild degree with narrowing of the lumen to about 50% in at least one place (cf Björk and Culhed 1969) and in one case narrowing of the right coronary artery at its origin from the aorta.

The aetiology of angina pectoris in AI, especially AI of rheumatic origin, has been the subject of much discussion. From autopsy studies Chasnoff and Silver (1951) and Coleman and Soloff (1970) have established that severe coronary arterial disease is a fairly common finding in patients over 40 years of age with rheumatic valvular heart disease. This has also been pointed out by Friedberg (1966) in discussions on the cause of angina pectoris in elderly patients with a relatively mild degree of AI. On the other hand, in reviewing non-selective coronary arteriograms from 60 patients with aortic valve disease, of whom 24 had pure AI, and 58 with mitral valve disease, of ages 16–69 years, Björk and Culhed (1969) found significant coronary arterial changes in only 2 patients—both with aortic valve disease. Of interest in this connection are the reports on the occurrence of severe angina pectoris in young patients under 30 years of age with advanced AI, with low diastolic pressures despite the absence of significant coronary arterial sclerosis or ostial narrowing (Harvey et al. 1957 Bland and Wheeler 1957 among others) It is a general opinion that the anginal pain in patients with AI without significant coronary arterial changes is due to a reduced effective coronary flow due to the low diastolic aortic pressure in combination with an increased need for blood supply to the hypertrophic left ventricle (Regan et al. 1956, Friedberg 1966, Karp and Roe 1966, and others) Of importance for the coronary circulation in AI is the decrease in the dominating coronary flow during diastole with, at the same time an increase during systole, shown in dog experiments (Green 1936 Hepps et al. 1963 Karp and Roe 1966, among others). In experimental AI in animals Bernsmeier (1965) found "fixed" coronary dilatation at rest with a diastolic coronary resistance which comprised 1/2 to 2/3 of the normal further dilatation during exercise may be impeded which would mean a reduced possibility of compensation for an increased load on the heart during exercise and in some cases might be responsible for the symptoms of coronary insufficiency A similar theory has been postulated by Karp and Roe (1966) who in their investigations of patients with chronic AI found a fixed maximal coronary flow

Dizziness especially on sudden changes of posture is a symptom which appears to have been seldom mentioned in the literature in descriptions of the symptoms in AI (cf Friedberg, 1966, however) It could be due to temporary cerebral ischaemia caused by rapid, pronounced pressure changes in the cerebral vessels at a high pulse pressure. It may be of interest, therefore, that among the 13 patients who were troubled by dizziness in the present series the pulse pressure was 100 or more in 11 patients on indirect measurement of the blood pressure in the arm and in 6 patients on direct measurement of the aortic pressure. In 6 of the 8 of these patients in whom angiographic determination of the total diastolic filling time for the left ventricle was possible, this time was shorter than 1 sec, thus indicating pronounced valvular incompetence.

Of the 18 patients with a history of subjective symptoms of *breathlessness* on effort (not including the pneumonectomized patient) *heart catheterization* revealed an elevated pressure in the left atrium and in the pulmonary artery at rest in just over half (10 patients including the 4 with additional MI) and in a further 4 patients with normal resting pressures there was a distinct pressure increase during subsequent exercise tests. This comparison between a patient's subjective symptoms and the objective findings is obviously difficult, one reason being that there is certainly in some cases a clear discrepancy between the sensation of dyspnoea on a certain degree of effort reported by the patient and the work load

chosen for the individual patient in connection with the pressure measurement, which in some of the patients probably was relatively too low All patients with indications of left ventricular failure in their history with the exception of one (No. 29) had an elevated left ventricular filling pressure at rest at the time of the catheterization.

Three of the 4 patients with a history of pronounced dyspnoea on effort, and whose activities were limited mainly by breathlessness, showed *signs of a mild to moderate ventilatory reduction* of the restrictive type in *lung function tests* The fourth patient had a normal maximal voluntary ventilation at both free and fixed frequencies, but the values for vital capacity and total lung capacity lay at the lower normal limit (75–80 per cent of the predicted values) These 4 patients had considerable cardiac enlargement, with a volume which in absolute figures varied between 1 400 and 1 550 ml, and in 3 patients the history indicated left ventricular failure, with pulmonary oedema in 1 of them. Of the remaining 14 patients (not including the pneumonectomized patient) with moderate dyspnoea on effort, only 2 (Nos. 31 and 89) had a ventilatory reduction of the restrictive type which was slight, and one further patient (No. 67) had a moderate obstructive ventilatory reduction. All of these 3 patients had a pronounced increase in the heart volume up to between 1 800 and 2 165 ml and a raised left ventricular filling pressure both at rest and during exercise. The results of the lung function tests will be reported later in a special section.

FUNCTIONAL CAPACITY AND EXERCISE TEST

I. *Functional classification*

The division of the patients into *different function classes* (see under Methods) within the *4 angiographic AI grades* and the *age distribution* within each function class, are shown in Table 3 Two-thirds of the patients, half of whom had pronounced aortic incompetence of grade IV managed the normal activities of life without limitations and 1/3 even managed to carry out heavy physical work. As expected, the patients with the two mildest grades of incompetence came under the latter category with the exception of one patient (No. 51) who after recurrent thrombosis

Table 3 *The age variations and distributions of the patients into AI grades I IV with respect to the functional classification*

Function class	Number of patients, AI Grade I	II	III	IV <45 y	IV ≥45 y	Total	Mean age (range) (years)
I	1	5	4	12	5	27	35.4 (18–58)
II		1	7	12	7	27	41.8 (18–62)
III A			2	4	11	17	47.0 (26–59)
III B			2	1	7	10	55 0 (38–62)
IV							

of the lower leg and a suspected pulmonary embolus during the last 9 months before the investigation was unable to manage heavy physical activities. He was also the oldest of these 7 patients—50 years of age. No patient had such a reduced functional capacity as to correspond to function class IV Of the 4 patients with AI_{III} who were assigned to function class III A or B 3 were between 59 and 62 years old. As is evident from Table 3 the functional capacity decreased gradually with an increasing mean age in the different function classes, but the age limits were wide.

II. *Exercise test*

The exercise test was performed by all patients with the exception of patient No. 105 with AI grade I, who had a foot injury and was unable to carry out the test. Table 4 gives a summary of the *highest (maximum) performed work loads* ($W_{max\ perf}$ defined under Methods) for all patients with different AI grades. As mentioned in the description of the methods the patients carried out a submaximal exercise test and the heart rate was allowed to rise to a maximum of about 170 beats/min. 45% of the men had a physical work capacity ($W_{max\ perf}$) of 900 kpm/min or higher The highest values, 1 400 and 1 350 kpm/min, were attained by 2 men with AI grade III who were 48 and 49 years old. About 1/3 (31%) of the women had a physical work capacity of 600 kpm/min or slightly higher

W_{70} (see under Methods in this chapter) could be calculated in a total of 36 patients (44% of the men and 50% of the women) 13 of whom, however were not in a circulatory steady state,

Table 4 *Physical work capacity expressed as the highest performed work load* ($W_{max\ perf}$) *with regard to sex and AI grades*

One male patient (No. 100) with left-sided pneumonectomy is included among the patients with AI grade IV above 45 years of age and with a physical work capacity of 300–449 kpm/min

	Number of patients									
	Male, AI grade					Female, AI grade				
$W_{max\ perf}$ (kpm/min)	II	III	IV <45 y	IV ≥45 y	Total	II	III	IV <45 y	IV ≥45 y	Total
150– 299				1	1			1	2	3
300– 449		1		3	4	1	2	2		5
450– 599		1		4	5		2		1	3
600– 749		3	7	9	19	1		3	1	5
750– 899	1		1	4	6					
900–1199	1	4	11	5	21					
1200–1500	2	2	4		8					

and W_{150} in 21 additional patients (27% of the men and 5% of the women) of whom 6 were not in a circulatory steady state. W_{80} was calculated in a further 13 patients (20% of the men) of whom 1 was not in a circulatory steady state. Only in one of the patients with AI grade II was it not possible to determine the physical work capacity at a pulse rate of 170 beats/min (No. 51). This patient was also the only man with AI grade II who did not manage a work load of 900 kpm/min. His physical work capacity was limited on account of muscular fatigue in the legs, a residual state following recurrent thrombosis of the legs. In patients with AI grades III and IV the mean work load ± S.E.M at a pulse rate of 170 beats/min was 908 ± 38 kpm/min for 25 men and 514 ± 65 kpm/min for 6 women.

The statistical values for the *highest performed work load* with the corresponding *heart rate* (HR_{max}) and for the "*work pulse*" i.e. the work in kpm/min per heart beat at $W_{max\ perf}$ are given in Table 5 for the male and female patients with different grades of AI. It was considered justifiable to calculate the physical work capacity per heart beat at the level of work intensity reflected by $W_{max\ perf}$, since it may be assumed that several other factors than the heart rate reaction may limit the physical work capacity in these cases, particularly with increasing age with the ensuing progression of the valvular disease and increasing frequency of subjective symptoms. At $W_{max\ perf}$ all patients with AI grades II and III and those under 45 years of age with grade IV both men and women, had a heart rate which lay on the average within the range 160–166 beats/min. On the other hand, for HR_{max} there was a highly significant difference of an average of 18 beats/min ($P < 0.001$) between the younger and older groups of male patients with AI grade IV. At rest before the exercise test no significant difference in heart rate was found between the age groups. Patients taking digitalis were more numerous, as expected, in the older than in the younger age group, these figures being 18 and 12 for the men and 4 and 2 for the women, respectively. The difference in $W_{max\ perf}$ between these two age groups was also highly significant ($P < 0.001$) and the difference in "work pulse" significant ($P < 0.01$). It is known from several studies of the normal population that the highest obtainable heart rate during exercise in the sitting position as well as the maximal circulation-limited bicycle work capacity decreases with increasing age (Robinson 1938, Åstrand 1952, Åstrand 1958 and 1960, Strandell 1964, Ericsson and Irnell 1969 *b* and *c*). The age-dependent decrease in maximal work capacity has usually been found to be closely related to the decrease in maximal heart rate, in normal individuals, so that the load at a given submaximal heart rate (e.g. W_{130}) remains constant. König et al. (1961) and in a longitudinal study on a population sample Ericsson and Irnell (1969 *b* and *c*) in contrast to other authors, found a decreasing physical work capacity even when expressed as a submaximal exercise capacity index (e.g. W_{130}).

Table 5 *Statistical values of the highest performed work load* ($W_{max\ perf}$) *and the corresponding heart rate* (HR_{max}) *and the ratio of* $W_{max\ perf}$ *to* HR_{max}

The patients are classified into AI of varying degrees and with regard to sex. One male patient (No. 85, AI_{III}) with a pacemaker implanted is not included

AI grade		$W_{max\ perf}$, kpm/min			HR_{max}, beats/min			$W_{max\ perf}/HR_{max}$, kpm/min per heart beat		
		Mean	S.E.M	Range	Mean	S.E.M.	Range	Mean	S.E.M.	Range
Males										
II	4	1 025		800-1200	165		147–176	6.2		5.1–7.5
III	10	895	95	465-1400	160	3	142 172	5.6	0.6	3.1–8.8
IV										
<45 y	23	875	43	600–1200	163	3	132 176	5.3	0.2	3.5–7 4
≥45 y	26	646	39	200– 940	145	4	104–174	4.4	0.2	1.9–5.9
Females										
II	2	500		400- 600	163		159–166	3.1		2.5–3.6
III	4	429		400- 470	163		146–175	2.6		2.4–2.8
IV										
<45 y	6	479		210- 670	166		146–183	2.9		1.3–4.0
≥45 y	4	390		200- 600	135		114–157	2.8		1 7–3.8

In the present series of patients with cardiac disease the purely age-dependent reduction of the circulatory functional capacity is difficult to evaluate, since other important factors such as the duration of the disease and the degree of severity of the valvular lesion with possible sec ondary myocardial disease probably play a decisive role. The 8 male patients in the series with a history of *left ventricular failure* (excluding patient No. 85 with a pacemaker) had the follow ing mean values $\pm$S.E.M. for $W_{max\ perf}$ HR_{max} and work pulse 521 ± 57 kpm/min 135 ± 8 beats/min and 3.8 ± 0.3 kpm/min per heart beat. In 37 male patients with AI grades III and IV and no evidence of left ventricular failure in their history and in whom an increase of the mean pressure in the left atrium to a maximum of 15 mmHg and an effective stroke volume of over 70 ml were noted during the exercise test, the corresponding values were 851 ± 34 kpm/min, 158 ± 3 beats/min and $5 4 \pm 0.2$ kpm/min per heart beat. For all these values there was a highly significant difference ($P < 0 001$) between the two groups of patients. A comparison was also made between the latter group of 37 patients and 8 other patients with AI grades III and IV in whom during the exercise test there was an increase of the left ventricular filling pressure (LA mean pressure, but in patients with AI + MI LV end-diastolic pressure) to over 20 mmHg and a stroke volume which did not exceed 70 ml (46–69 ml) and which decreased in 6 patients, which may be regarded as a rough indication of a probable impairment of the myocardial function. Four of these patients also had signs of left ventricular failure in their history The mean differences between these two groups were 305 kpm/min for $W_{max\ perf}$ 1.6 kpm/min per heart beat for work pulse and 14 beats/min for HR_{max} the two former differences were highly significant ($P < 0.001$) and the third probably significant ($P < 0 05$)

One of the patients (No. 85), in whom a fixed-rate pacemaker with frequency of 70 beats/min had been implanted on account of atrioventricular blocking of varying degrees, managed work load of 300 kpm/min with constant ventricular frequency at an atrial frequency of 105/min. Since the patient had shown signs of left ventricular failure and had had few attacks of pulmonary oedema despite the pacemaker therapy and cardiac therapy the effect of an increased pacemaker frequency was tested; with this it was expected that shortened diastole would be achieved, with an ensuing reduction of the regurgitation volume and of the load on the left ventricle. After the patient had been connected to an external impulse generator with frequency of 87/min for 5 days there was marked subjective improvement, with less respiratory distress at night and on effort. The diuresis also increased by about 0.5 litres/24 hours. The highest performed work load was now somewhat higher namely 370 kpm/min at an atrial frequency of 125/min. The respiratory and blood pressure reactions in the exercise test were essentially the same at these two pacemaker frequencies.

Table 6. *Comparisons between functional classification and physical work capacity* ($W_{max\ perf}$) *with the corresponding heart rate* (HR_{max}), *and the ratio of* $W_{max\ perf}$ *to* HR_{max} *in male and female patients*

One male patient (No. 85) with pacemaker, in function class III A, is not included

Function class		$W_{max\ perf}$, kpm/min			HR_{max}, beats/min			$W_{max\ perf}/HR_{max}$ kpm/min per heart beat		
		Mean	S.E.M	Range	Mean	S.E.M.	Range	Mean	S.E.M.	Range
Males										
I	20	920	55	600–1400	167	2	142 176	5.5	0.3	3.5–8.2
II	21	867	41	600–1350	155	3	117–176	5.6	0.2	4.1–8.8
III A	15	653	54	200– 940	149	5	104–171	4.3	0.3	1.9–5.9
III B	7	509	55	300– 740	135	7	121–170	3.7	0.3	2.5–4 7
Females										
I	6	578		400– 670	165		157–183	3.5		2.5–4.0
II	6	442		400– 540	164		146–180	2.7		2.2 3.5
III A	2	306		210– 400	153		146–160	2.0		1.3–2.7
III B	2	213		200– 230	115		114–115	1.9		1 7–2.0

The favourable effect of *tachycardia* in patients with *AI* has been studied and confirmed by several investigators, who have increased the heart rate by electrical stimulation of the right atrium. This will be discussed in the chapter on haemodynamics (chapter V p 60)

The *relationship* between *functional grading* on the basis of *subjective symptoms* and objective evaluation of the *physical work capacity* can be seen in Table 6. In function class I the highest performed work load for all except 4 of the men was 900 kpm/min or higher and for all women except one 600 kpm/min or higher In function class II 11 of the men managed to work against a load of 900 kpm/min or more but none of the women managed 600 kpm/min and only one managed more than 500 kpm/min. The patient who showed a maximum performed physical work load of 1 350 kpm/min at HR_{max} 153/min and a respiratory frequency of 40/min and who nevertheless was assigned to function class II, had a history of marked subjective symptoms in the form of a sensation of pressure over the chest, difficulty in obtaining air a dry cough and palpitations on performing heavy physical work, especially with rapid sudden movements. This symptoms were partly provoked at the start of a second exercise test, at which test 1 200 kpm/min was chosen as the initial work load.

The *exercise tests* were *terminated* in the individual cases for different reasons, which were partly related to the function classes. Thus in 24 of 26 patients in function class I the test was terminated because of the heart rate reaction, while this was the reason in only about half of the patients in function class II, only in about a quarter of those in function class III A and in no patient in function class III B The reason for termination of the test in 19 patients was a sensation of breathlessness and a respiratory frequency of 30–40 breaths/min (one of these patients was No. 100 with a left pneumonectomy), in 10 patients general fatigue, in 5 patients a large increase in the systolic arterial blood pressure towards 300 mmHg and in 1 single patient from function class III A a decreasing systolic arterial pressure at the highest work load, followed by supraventricular and ventricular arrhythmia and ECG changes of the type seen in coronary insufficiency

HEART VOLUME

In Tables 7 and 8 the results of the heart volume determinations in the standing position are presented. The total volume of the heart is given both in absolute values and in values related to the body surface area, a mode of calculation which has long been used for routine purposes, and which has been considered by several authors, e g. Jonsell (1939) and Maurea et al. (1955) to facilitate intra- and inter-individual comparisons. These authors, as well as Liljestrand et al. (1939) have also reported normal values for the heart volume obtained in the sitting and

Table 7 *Total heart volume in the standing position given in absolute values (ml) and relative values (ml/m² body surface area) in male and female patients with varying degrees of AI*

BSA = body surface area. One male patient (No. 100) is not included as it was impossible to define the left heart contour owing to anatomical changes after left-sided pneumonectomy

AI grade		Total heart volume: Absolute values (ml) Mean	S.D	S.E.M.	Range	Relative values (ml/m² BSA) Mean	S.D	S.E.M.	Range
Males									
II	4	935	—	—	845–1 090	466	—	—	405– 535
III	11	1 320	281	85	955–1 675	695	106	32	530– 830
IV									
<45 y	22	1 234	291	62	830–1 960	648	129	28	425– 985
>45 y	22	1 439	338	72	990–2 440	755	181	38	515–1 325
IV ≶45 y	44	1 336	328	49	830–2 440	701	164	25	425–1 325
IV+MI	4	1 428	—	—	1 190–1 895	759	—	—	620–1 010
Females									
I	1	645	—	—	—	370	—	—	—
II	2	755	—	—	580– 930	448	—	—	385– 510
III	4	726	—	—	535– 950	445	—	—	340– 565
IV									
<45 y	6	1 038	—	—	590–1 600	608	—	—	340– 955
>45 y	3	1 227	—	—	1 015–1 455	703	—	—	550– 855
IV ≶45 y	9	1 101	318	106	590–1 600	640	190	63	340– 955
IV+MI	1	1 230	—	—	—	695	—	—	—

standing postures. Sometimes the heart volume has been related to body weight instead of body surface area (Reindell 1964 Reindell et al. 1967 *b*). In a recent study of 85 elderly persons (58–86 years old) with no apparent heart disease Bäcklund et al. (1972) have found that the heart volume, as a rule, was better correlated to the body weight than to the calculated body surface area.

I. *Heart volume in relation to AI grades*

In persons with no heart disease it has been found at this hospital, as well as in most other roentgenological departments in Sweden (Bergström and Erikson 1971) that the relative heart volume in the upright position does not usually exceed 500 ml/m² body surface area in men and 450 ml/m² in women. Assuming these values as the upper normal limit, altogether 10 of the patients (12 %) of the present series could be said to have a normal-sized heart (viz the patient with AI grade I, 4 of the 6 patients with AI grade II 2 patients with AI grade III and 3 with AI grade IV below 45 years of age). A further 6 patients with AI grade IV had only slight enlargement of the heart (relative heart volume for men less than 550 ml/m² body surface area and for women less than 500 ml/m²) and also one patient with AI grade III and one with AI grade II. The female patient with AI grade II and a relative heart volume of 510 ml/m² had had myocarditis about one year before the investigation at this hospital, which may have contributed to her cardiac enlargement. Cardiac enlargement with a relative heart volume of over 700 ml/m² was found in 31 of the patients, corresponding to 39 % of the series (the absolute heart volume in these cases was more than 1 200 ml) 4 of these patients had AI grade III and the remaining 27 grade IV Of the 31 patients 17 had a relative heart volume of over 800 ml/m² (the absolute heart volume in these cases was more than 1 400 ml) and 3/4 were over 45 years old.

The results obtained from a comparison of the different AI grades are difficult to evaluate, since some groups comprise only a few observations. This applies generally to the female patients, and therefore the findings from this group allow no definite conclusions. For the male patients there is a significant difference in the relative heart volume between AI grades II and III ($P < 0.01$) and a probably significant difference for the absolute volume ($P < 0.05$) while there is no signifi-

cant difference in these respects between AI grades III and IV nor between the patients with AI grade IV with and without MI. A comparison between the younger and older age groups with AI grade IV on the other hand, showed that the heart volumes were probably significantly larger ($P < 0.05$) in the older patients

II. *Heart volume in relation to functional classification*

Wilson and Lim (1957) found a positive correlation between the heart volume and mortality in mitral and aortic valvular lesions and pointed out the prognostic importance of the heart size in these cases. Since the largest heart volumes are often found among patients with AI and since it has been found, as mentioned previously that these patients are often free for a long time from symptoms that limit their normal activities, it seemed of interest to compare the heart size and functional classification in patients of the present series (Table 8). Only patients with the more pronounced grades of incompetence III and IV are included in this table, as the valvular lesions in these cases could be assumed to be mostly of such a degree as to lead to fairly marked haemodynamic changes. Not unexpectedly a tendency to a progressive decrease in the functional capacity was found with an increase in the heart volume. Twenty-four (92 %) of the 26 male and female patients with a relative heart volume of up to 600 ml/m² body surface area belonged to function class I or II, while the corresponding figure for the group with a heart volume of 600–700 ml/m² was 63 % and in patients with relative heart volumes between 700 and 1 000 ml/m² body surface area the figure remained constant at 42–50 % with every increase of 100 ml. It is worthy of observation that as many as half of the patients with a heart volume of between 800 and 1 000 ml/m² body surface area managed the normal activities of life with no limitations.

III *Heart volume in relation to physical work capacity*

The relationship between heart volume and different measures of circulatory function has been demonstrated by several investigators. As has been pointed out by Sjöstrand (1950, 1953) by studying the relationship between physical work capacity and total haemoglobin or heart volume

Table 8 *Relative heart volume expressed as ml/m² body surface area, in males and females with AI grades III and IV with respect to the functional classification*

BSA = body surface area. One male patient (No. 100) is not included as it was impossible to define the left heart contour owing to anatomical changes after left-sided pneumonectomy

Heart volume standing (ml/m² BSA)	Function classes (No. of pats.) I	II	III A	III B	Total
Males					
≤ 500	1	1			2
> 500– 600	6	9	1		16
> 600– 800	8	6	7	5	26
> 800–1 000	2	4	4	2	12
> 1 000–1 400			2	1	3
Females					
≤ 450	1	2			3
> 450– 600	2	2	1		5
> 600– 800	1	1	1	1	4
> 800–1 000		1		1	2

more complete information can be obtained on circulatory function and circulatory adaptation to work, both in normal persons and in patients with heart disease. In a normal person the heart size (best in the supine position) is correlated to different measures of circulatory function, such as total haemoglobin and physical work capacity as shown by Kjellberg et al. (1949) Sjöstrand (1950) and Holmgren et al. (1960) and also to maximal oxygen uptake and maximal oxygen pulse (König et al. 1961 Reindell et al. 1967 *b* Schleusing et al. 1968) In healthy subjects there is also a direct correlation between stroke volume and heart volume, as reported by Holmgren et al. (1960) and Reindell et al. (1967 *b*).

As has been shown by Bergström (1969) and other authors, the method which has come into use for determination of the heart volume has great importance for the comparison between the heart volume and different parameters of circulatory function. From a circulation-physiological aspect the supine or prone position for heart volume determination is preferable to sitting or standing, as orthostatic reactions of varying degree affect the venous return to the heart in the upright position, with an ensuing decrease of the heart volume (Bjure and Laurell 1927/28, Larsson and Kjellberg 1948 Holmgren and Ovenfors 1960 Bergström et al. 1969 *a*) In a comparison between the heart volume and different circulatory para-

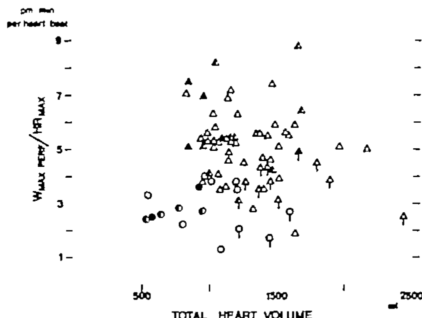


Fig. 3 Relationship between the total heart volume (ml) and the maximal performed work load per heart beat (expressed in kpm/min per heart beat). Circles indicate females. Triangles indicate males. Filled symbols = AI grade II half-filled symbols = AI grade III open symbols = AI grade IV; symbols marked with line indicate patients with history of left ventricular failure and/or an increase of the left ventricular filling pressure to over 20 mmHg during an exercise test and an effective stroke volume of less than 70 ml.

meters in healthy young men, however Bergström et al. (1969 *b*) found the same correlation ($r = 0.58$) between W_{170} and heart volume in the sitting and supine positions, using Jonsell's formula. Since, as mentioned under Methods heart volume determination in the supine position was only performed in less than half of the patients of the present series, it has been considered appropriate for the sake of uniformity to present only the results of the examinations in the standing position, which comprise all patients (with the exception of patient No. 100 in whom the contour of the heart could not be defined owing to anatomical changes following left-sided pneumonectomy).

In patients with organic heart disease it has been found that the normal *relationship* between *physical work capacity and heart volume* is not seldom altered (Kjellberg et al. 1949 Holmgren et al. 1957 Reindell et al. 1967 *b* Schleusing et al. 1968) the physical work capacity becoming low in relation to the heart olume This is illustrated in Fig. 3 where the *heart volume* in the standing position, expressed in absolute figures, has been *correlated* to the *work pulse* ($W_{max\ perf}/HR_{max}$)

The 8 patients with a history of left ventricular failure (7 men and 1 women) all had a total heart volume of over 1 200 ml (corresponding to about 700 ml/m² body surface area or higher) and all the men except one showed a work pulse of 4.5 kpm/min per heart beat or lower Eleven patients (8 men and 3 women) in this lower right hand side of the Figure, with a large heart volume and a relatively low work pulse had during heart catheterization at a fairly low work load a LV filling pressure of more than 20 mmHg and an effective stroke volume which was lower than 70 ml (in 9 cases below 60 ml) and which decreased durmg exercise in 7 patients. Five of these 11 patients also had a history of left ventricular failure. These 14 patients with LV failure in their history and/or haemodynamically are indicated in the Figure by a vertical line

The male patient (No. 24) with the lowest "work pulse (1.9 kpm/min per heart beat) showed, at rest, a raised mean PCV pressure of 30 mmHg and a relatively low stroke volume of 59 ml. On account of severe angina pectoris he was unable to carry out any exercise test during the catheterization. A further 2 male patients (Nos. 50

and 72) in the lower right-hand side of the Figure, with work pulses of 2.8 and 3.9 kpm/min per heart beat, respectively were suspected to have had myocarditis apart from their valvular lesion. The female patient (No. 102) with the lowest "work pulse (1.3) had a hypokinetic circulation with an elevated arterio-venous oxygen difference and a low stroke volume of 40 ml at rest and during the exercise test at a work load of 100 kpm/min when the LV filling pressure rose from the normal resting value to a slightly raised level. Four of the 5 patients with concomitant MI are also found in this lower right-hand side of the Figure. It is seen, further from the Figure that a number of patients could have a good functional capacity despite considerable enlargement of the heart. In these cases the cardiac enlargement would seem to have been mainly due to the increased volume load on the left ventricle caused by the regurgitation.

Thus it is evident that a study of the relationship between heart size and physical work capacity in cases with AI might provide information on the functional capacity of the myocardium. The importance of such a correlation between the heart volume and a parameter of circulatory function for an evaluation of possible myocardial insufficiency has been pointed out by Reindell et al. (1967 *b*) in their studies of the relationship between heart size and maximal oxygen pulse in healthy subjects and patients with heart disease and also by Schleusing et al. (1968) in their analysis of the essential difference between cardiac enlargement in well-trained healthy subjects and patients with different kinds of heart diseases (including 17 men and 6 women with AI). This analysis was based on a study of the correlation between heart volume, on the one hand, and maximal oxygen uptake and maximal oxygen pulse, on the other

LUNG FUNCTION TESTS

The values for *ventilatory capacity* and *total lung capacity expressed in per cent of the predicted* normal alues, are presented in Table 9 These normal" values, which are based on data from a study carried out in Gothenburg (published 1963 as mentioned under "Methods") and which refer to normal subjects of ages 7–70 years, lie at a somewhat higher level than the values obtained by Ericsson and Irnell (1969 *a*) in apparently healthy persons of ages 52–71 years in a population sample, investigated in the same laboratory as the patients of the present series.

In pronounced AI a considerable enlargement of the heart is frequently found, and also fairly often, an elevated left entricular filling pressure. Hence, it might be expected to find a ventilatory reduction of the restrictive type in these patients.

According to Berglund and Söderholm (1963) every form of ventilatory reduction which is not due to increased airway resistance should be described as *restrictive* and that which is due to increased airway resistance should be described as *obstructive* (cf also Comroe et al. 1964).

I. *Lung function and AI grades*

The patients with the two lowest grades of aortic incompetence had normal values (80% or more of the predicted values) with the exception of patient No. 19 who had moderately reduced values for maximal voluntary ventilation (50–69% of the predicted values) both at a free and fixed frequency but otherwise normal values. With a high degree of probability the MVV reductions were due to poor technical performance or poor cooperation, since the value for MVV_F according to the equation given by Grimby and Soderholm (1963) was lower than there was reason to expect from the normal value in question for $FEV_{1.0}$. The same finding was made in 10 further patients, 2 of whom had AI grade III and 8 AI grade IV Of the remaining patients, 20 (18 men and 2 women, not including the pneumonectomized patient) had a ventilatory reduction, which in 17 patients was restrictive (VC less than 80% of the predicted values) in 2 obstructive (FEV and FEV% less than 80% and the residual olume in proportion to the total lung capacity 120% of the predicted values or larger) and in 1 a combination of obstructi and restrictive. Most of these patients (16) had AI grade IV and the rest grade III. It is of interest that 4 of the 5 patients with concomitant mitral incompetence had practically normal lung function values.

II. *Restrictive ventilatory reduction*

Included in the group with restrictive ventilatory reduction were 2 men and 1 woman (Nos. 24 48



Fig. 3. Relationship between the total heart volume (ml) and the maximal performed work load per heart beat (expressed in kpm/min per heart beat). Circles indicate females. Triangles indicate males. Filled symbols = AI grade II, half-filled symbols = AI grade III, open symbols = AI grade IV, symbols marked with line indicate patients with history of left ventricular failure and/or an increase of the left ventricular filling pressure to over 20 mmHg during an exercise test and an effective stroke volume of less than 70 ml.

meters in healthy young men, however Bergström et al. (1969 *b*) found the same correlation (= 0.58) between W_{70} and heart volume in the sitting and supine positions, using Jonsell's formula. Since, as mentioned under "Methods" heart volume determination in the supine position was only performed in less than half of the patients of the present series, it has been considered appropriate, for the sake of uniformity to present only the results of the examinations in the standing position, which comprise all patients (with the exception of patient No. 100 in whom the contour of the heart could not be defined owing to anatomical changes following left-sided pneumonectomy).

In patients with organic heart disease it has been found that the normal *relationship* between *physical work capacity and heart volume* is not seldom altered (Kjellberg et al. 1949 Holmgren et al. 1957 Reindell et al. 1967 *b* Schleusing et al. *1968) the physical work capacity becoming low* in relation to the heart volume. This is illustrated in Fig. 3 where the *heart volume* in the standing position, expressed in absolute figures, has been *correlated* to the *work pulse* ($W_{max\ perf}/HR_{max}$)

The 8 patients with a history of left ventricular failure (7 men and 1 women) all had a total heart volume of over 1 200 ml (corresponding to about 700 ml/m² body surface area or higher) and all the men except one showed a "work pulse" of 4.5 kpm/min per heart beat or lower. Eleven patients (8 men and 3 women) in this lower right hand side of the Figure, with a large heart volume and a relatively low work pulse had during heart catheterization at a fairly low work load a LV filling *pressure of more than 20 mmHg* and an effective stroke volume which was lower than 70 ml (in 9 cases below 60 ml) and which decreased during exercise in 7 patients. Five of these 11 patients also had a history of left ventricular failure. These 14 patients with LV failure in their history and/or haemodynamically are indicated in the Figure by a vertical line.

The male patient (No. 24) with the lowest "work pulse" (1.9 kpm/min per heart beat) showed, *at rest, a raised mean PCV pressure of* 30 mmHg and a relatively low stroke volume of 59 ml. On account of severe angina pectoris he was unable to carry out any exercise test during the catheterization. A further 2 male patients (Nos. 50

III. *Ventilatory reduction of mixed type*

As mentioned previously the lung function studies in 2 patients revealed an *obstructive* type of ventilatory defect. One patient (No. 67) who smoked 20 cigarettes daily had an obstructive ventilatory insufficiency of moderate degree, and in patient No 44 with bronchial asthma there were signs of hyperinflation. Patient 83 who had a reduced ventilatory capacity of both the *restrictive and obstructive type* had previously had symptoms of bronchitis. In addition he had considerable enlargement of the heart, with an absolute heart volume of 1 510 ml.

The pneumonectomized patient

One of the male patients with AI grade IV (No 100) 57 years old, who is not included in Table 9 had undergone left pneumonectomy f cystic disease of the lung 13 years before the investigation at this hospital. In addition, he had healed lesions on the right lung following pulmonary tuberculosis, roentgenologically consisting of small striated areas of density in the apical region and minor pleural changes. The patient had recovered well after the lung operation and experienced the dyspnoea on effort as only moderately disabling. Lung function studies revealed signs of marked ventilatory defect of both restrictive and obstructive type; VC = 54% FEV = 47% MVV = 30% MVV_{ind} = 37% TLC = 47% and RV = 48% of the predicted normal values for both lungs.

The values for FEV% and for the maximal expiratory flow rate were markedly reduced. The residual quotients (functional residual capacity/total lung capacity and residual volume/total lung capacity) were normal, as was the intrapulmonary air mixing evaluated by the helium dilution method. The pulmonary vascular resistance was elevated, the resting value being 3 9 mmHg per l/min. At rest, the patient had low arterial oxygen saturation (83%) and arterial P_{O_2} (51 mmHg) and high arterial P_{CO_2} (58 mmHg) and these values remained unchanged at work load of 200 kpm min.

It seems certain that in this case both pre existing pathological changes in the right lung and cardiac f ctors contributed to the ventilatory insufficiency which was accentuated further by the pneumonectomy This renders an evaluation of the findings difficult, and they will not therefore be analyzed more closely as this cannot lead to any definite conclusions.

In pneumonectomized patients with a normally functioning remaining lung and no heart disease, several uthors have found, in lung function studies at intervals of up to 15 years after the lung operation a moderate compensatory overinflation of the remaining lung with an increased residual volume and a reduction of the total lung capacity This was less than that corresponding to the loss of one lung. Further there was a practically normal arterial oxygen saturation at rest which decreased very slightly below the normal value during exercise (Birath et al. 1947 Harrison et al. 1958 Burrows et al. 1960 among others)

Except in the patients with an obstructive re duction of the ventilatory capacity the values for FEV% were normal and in 43 patients higher than the normal values.

IV *Ventilatory eduction and pulmonary vascular esistance*

Some relationship between an increased pulmonary vascular resistance and a decreased ventilatory capacity would seem conceivable. In 5 of the 13 patients with pure AI and without ankylosing spondylitis who had a restrictive ventilatory reduction the pulmonary vascular resistance at rest was over 2 (2.1-4 9) mmHg per l/min. There was a history of left ventricular failure in 3 of these 5 patients (Nos. 29 42 and 85) as well as in 2 other patients, one (No. 67) with an obstructive reduc tion of the ventilatory capacity and one (No. 83) with combination of the obstructive and restric tive types. The mean value for the pulmonary vascular resistance in these 5 patients was 3 4 (2.2–4.9) mmHg per l/min. In a further 9 pa tients with no ventilatory reduction the pulmonary vascular resistance at rest was over 2 mmHg per l/min, with a mean value of 2.5 (range 2.1–2.9) mmHg per l/min. Thus it does not seem possible to draw any definite conclusions from the above data concerning the possibility of a relationship between increased pulmonary vascular resistance and decreased ventilatory capacity

V *Ventilatory reduction and heart size*

A priori it might be expected to find patients with a large degree of cardiac enlargement among those with a restrictive ventilatory reduction. With one exception all of the 12 male patients with a respiratory alteration of this kind had a total heart volume of over 1 200 ml. The mean value ±S.E.M. was 1 545 ± 113 (range 1 065–2 440) ml this mean value is significantly greater ($P < 0.01$) than the mean value for 36 men with pure AI grades III and IV without ventilatory reduction and also significantly greater than that for the previously mentioned 8 men with decreased val-

ues for maximal voluntary ventilation which were probably due to poor cooperation In these cases the mean ±S.E.M was 1 004±57 (830–1 355) ml. The mean age of the latter group was 36 9 (range 27–45) years, and of the group of 12 male patients with a restrictive reduction of the ventilatory capacity 47 1 (18–62) years, but this age difference is not statistically significant.

CONCLUSIONS

The patients with the two mildest grades of aortic incompetence had no or few mild, not incapacitating symptoms in the form of ectopic beats, throbbing of the heart and strong pulsations in the peripheral parts of the body on physical effort these were the most common of all symptoms occurring in those patients in function class I who were not completely symptom-free. These patients with AI grades I and II had no or in a few cases very slight, enlargement of the heart. They had no ventilatory reduction either of the restrictive or the obstructive type.

Sixty-four per cent of the patients with the more pronounced grades of incompetence, III and IV managed to carry on the normal activities of life without limitations, and 15% of these had considerable cardiac enlargement with a relative heart volume of over 800 ml/m² body surface area. With increasing age and in more advanced stages of the disease there was a tendency to an increased number of symptoms and the addition of more severe, more disabling symptoms such as pronounced dyspnoea on effort, dry cough, angina pectoris, consequences of left and right ventricular failure such as functional reduction and limitation of the physical work capacity as well as a tendency to an increasing heart size.

Highly significant differences in the physical work capacity and "work pulse (work per heart beat) were found in a comparison between on the one hand patients with a normal left ventricular filling pressure and a normal effective stroke volume during an exercise test, and on the other hand patients with a history of left ventricular failure and/or a raised left ventricular filling pressure and a reduced effective stroke volume during an exercise test. The lower values were found in this latter group of patients, who apparently had poorer myocardial function. In a study of the relationship between the total heart volume and the "work pulse it was found that this latter category of patients with signs of impaired myocardial function had a low work pulse in relation to the large heart volume, as compared with patients without myocardial insufficiency Thus it seems that the comparison between heart size and physical work capacity expressed as "work pulse contributes to information on the functional capacity of the myocardium.

It appears that the subjective symptoms of dyspnoea on effort have a closer relationship to elevated left ventricular filling pressure than to restrictive ventilatory reduction as demonstrated by lung function tests. Neither does such ventilatory reduction seem to have a close relationship to increased pulmonary vascular resistance on the other hand, it showed some negative relationship to heart size.

IV PHYSICAL SIGNS AND ELECTROCARDIOGRAPHIC FINDINGS

METHODS

Physical signs

1 *Physical cardiac signs* were evaluated with respect to (1) the palpatory findings concerning the presence of a thrill and the nature of the apex beat, and (2) the auscultatory findings.

Palpatory signs of left ventricular hypertrophy were considered to be present if the apex beat was at least two fingers in breadth and heaving.

The *auscultatory findings* to which attention was mainly paid were the intensity of the second heart sound (aortic component) and the occurrence of a third heart sound and systolic and diastolic extra sounds. The occurrence of a fourth heart sound was judged from the phonocardiogram. The site and transmission as well as the intensity and the duration of the systolic and diastolic murmurs were noted. The intensity of the murmurs was graded from 1 to 6 according to Levine and Harvey (1959)

Information supplementary to the auscultatory findings was provided by phonocardiographic recordings.

2. *Peripheral signs.* The peripheral pulses were palpated and evaluated, especially the carotid arteries, according to the presence and quality of the waterhammer and collapsing pulse, i.e. *pulsus celer et magnus.* The following signs were also noted. *marked visible pulsations* in the neck vessels; *capillary pulsations,* by observing the nail bed *palmar click* *femoral arterial sound* (pistol shot sound)

Blood pressure

The indirect blood pressure was measured in both arms and both legs with a mercury manometer with the patient first supine and then prone. For the blood pressure measurements in the arm sphygmomanometer cuff with a rubber bladder 12 cm wide and about 30 cm long was used, and in the thigh a rubber bladder 18 cm wide and 60 cm long The diastolic pressure was determined both at the onset of muffling and at the disappearance of the Korotkov sounds (Ström and Werkö 1958 Kirkendall et al. 1967). The indirect systolic and diastolic pressures were noted to the nearest 5 mmHg. Duplicate determinations were made and in general the same value was obtained, but if there was any difference the mean value was used. When comparing the directly measured central aortic pressure and the indirect brachial arterial pressure, the pressure obtained from the right arm was used in cases where there was any difference between the two sides. When *comparing the indirectly with the* directly measured brachial and femoral arterial pressures, the pressures obtained by the two methods on the same side were used.

Phonocardiogram (PCG)

The calibrated phonocardiogram was recorded with a phonoamplifier and a dynamic microphone on the same direct writing four-channel ECG apparatus (Mingograf 42 or 34) as the ECG Filters with nominal frequencies of 25 c/sec and 100 c/sec and one auditory filter (Kjellberg et al. 1959 Strandell 1967) were used. The recordings were always made over the apex and over the 4th, 3rd and 2nd left and the 2nd right intercostal spaces at the sternal border with the patient in the supine position, during apnoea after normal expiration and over the 3rd and 4th left intercostal spaces and sometimes also over the 2nd right intercostal space in full expiration with the patient sitting and leaning forward. Supplementary recordings were made from the areas over the carotid arteries in patients with an AS-like murmur and over the apex with the patient lying on his left side in those with an MI-like murmur The paper speed was 100 mm/sec.

Evaluation of the electrocardiogram (ECG)

The apparatus and technique used in recording of the ECG at rest and during exercise have been

described in detail under Methods in chapter III (p. 18).

For evaluation of the ECG pattern the following method of measurement was used.

The *P R interval* was measured from the onset of the P wave to the beginning of the QRS complex.

The *ventricular activation time* (VAT) was measured from the beginning of the QRS complex to the peak of the R wave.

The *voltage of the QRS complex* was measured from the upper margin of the iso-electrical line to the peak of the R wave, and from the lower margin to the nadir of the S wave which latter procedure was also used in measurements of the *negativity of the T wave*. *Depression of the S-T segment* was also measured from the lower margin of the iso-electrical line.

The measurements were made on at least 3 ECG complexes and the respective mean values were calculated. Generally the standardization of the amplitude was set such that 1 mV corresponded to 10 mm, but in cases with high QRS voltages the amplification was reduced so that 1 mV corresponded to 5 mm.

Special attention was paid to the following ECG features:

1. The P R interval in the standard leads (I–III)
2. The sum of the S wave in V_1 and V_2, respectively and the R wave in V_5.
3. The sum of the S and R waves in that lead of V_{1-7} which gave the highest QRS voltage, called max. QRS voltage.
4. The maximum VAT among leads V_5, V_7 or aVL.
5. The S-T segment and the T wave in V_5 and V_7. Consideration was taken here both of the degree of S-T depression and the T wave negativity and of the nature of the ST T changes.

During the exercise test a rough evaluation of the S-T depression and T wave change was made, but no precise gradation. Any arrhythmia during and after the exercise test was also noted.

PHYSICAL SIGNS

In pure AI the clinical findings are generally so unequivocal that there are seldom any major diagnostic difficulties (Frank et al. 1965, Grosse-Brockhoff and Loogen 1965 among others). However the signs of aortic incompetence can subside or disappear for example in congestive heart failure (Gorlin and Goodale 1956, Stapleton and Harvey 1969) or in the presence of other valvular lesions (Runco et al. 1961, Segal et al. 1964, Cohn et al. 1967). In these cases further investigations, particularly thoracic aortography are required to establish the diagnosis and evaluate the degree of severity of the incompetence.

The characteristic cardiac and peripheral signs in AI are well known. The pulse in AI was first described as early as in 1715 by Vieussens (Major 1945) and later in more detail by Hope (1839). In his classical comparison between the clinical and pathological findings in AI, Corrigan (1832) drew attention to the visible carotid pulsations, which now go under the name Corrigan pulse. Another pulse phenomenon in AI is the double femoral murmur which was described by Duroziez in 1861. An apical mitral diastolic murmur —suggestive of mitral stenosis—in aortic incompetence which goes under the name "Austin Flint's murmur" was observed by Flint in 2 patients and was described by him in 1862. Accounts of original descriptions of AI are given by Major (1945) and Adams (1969).

I. *Cardiac Signs*

In Table 10 the physical cardiac findings are summarized in relation to the different grades of AI and to AI_1 combined with MI.

1. *Palpable left ventricular hypertrophy.* Of the 30 patients with a strongly heaving apex beat of more than 2 finger-breadths, 25 had ECG signs of left ventricular hypertrophy which according to the criteria given on p. 53 were assessed as typical in 20 patients, as probable in 3 and as suspected in 2. Among the other 27 patients with palpable left ventricular hypertrophy in the form of a heaving apex beat of 2 finger-breadths, 21 had ECG changes which were classified as typical left ventricular hypertrophy in 16 cases and as probable in 5 cases. Of the patients with AI_1, 12% of the 17 patients in the sub-group $AI_{IV<1}$ had palpable left ventricular hypertrophy of the "ictus + +" type while this finding was only made in 4% of the 13 patients with $AI_{IV>1}$.

2. *Heart sounds.* Of the 6 patients (Nos. 24, 29, 41, 50, 75, 85) in whom auscultation revealed a

Table 10 *Physical cardiac findings in isolated AI of varying degrees and in AI grade IV combined with MI of a slight to moderate degree*

	Number of patients						
	AI grade						
Physical signs	I	II	III	IV	IV + MI	Total No.	%
Palpable LVH							
ictus +			9	17	1	27	33
ictus + +			1	25	4	30	37
2nd sound							
faint			1	5		6	7
ordinary		5	9	19	2	35	43
accentuated	1	1	5	30	3	40	49
3rd sound			4	11	3	18	22
4th sound			1	3	1	5	6
Systolic click		3	2	9	1	15	19
Systolic murmur							
over the base							
ejection type							
intensity 2–3		1	7	31		39	48
intensity 4–5			3	20		23	28
over the apex							
regurgitant type							
intensity 3–4			1	10	4	15	19
Diastolic murmur							
intensity 1 2		3	6	12		21	26
3–4	1	3	9	41	5	59	73
5				1		1	1
max point							
3–4L		1	8	27	2	38	47
1–3R		1	4	15	2	22	27
2R 3L			2	10	1	13	16
2L	1	4	1	2		8	10
duration							
< ½ diastole		4	3	8	1	16	20
> ½ diastole		1	2	17	2	22	27
holodiastolic	1	1	10	29	2	43	53
Total number of patients	1	6	15	54	5		

LVH = left ventricular hypertrophy
Palpable LVH, ictus + = heaving apex beat of 2 finger-breadths.
ictus + + = markedly heaving apex beat of more than 2 finger-breadths.
2nd, 3rd and 4th sound = second, third and fourth heart sound.
Max. point the point of maximal intensity of the diastolic murmur
L left intercostal space at the sternal border
R right intercostal space at the sternal border

weakened second sound (aortic component) one (No 24) had generally weak heart sounds. In the other 5 patients the sound could not be distinguished with certainty from the murmurs in the phonocardiogram (PCG). These 6 patients, whose mean age was 53 7 (48–62) years, were all in an advanced stage of the disease with considerable enlargement of the heart—the mean total heart volume was 1 675 (1 320–2 440) ml and the relative heart volume was 911 (705–1 327) ml/m² body surface area. Two of these 6 patients (Nos. 29 and 85) had a history of left ventricular failure one (No. 85 with AI $_{II}$) had an implanted pacemaker A third patient (No. 4) had severe angina pectoris and a fourth (No. 50) had had myocarditis one year prior to the investigation at this hospital Four of the patients were in function class III A or B Only in one case had angio-

graphy shown reduced mobility of the aortic valve leaflets. No calcifications were observed on the angiograms in any of these cases.

The patients with an *accentuated second sound* (aortic component) had a lower mean age of 40 (18–60) years and 3/4 of them were in function class I or II. In 3 of these patients a very strong second sound was heard over the 2nd right intercostal space. In one of these 3 (No. 83) a 60-year-old man with AI_{III} of unknown aetiology and with a murmur which had been detected less than one year previously the second sound was clearly palpable over the 2nd right intercostal space and could be heard distinctly on the neck and out along the back. At angiocardiography the valve leaflets were seen to be clearly thickened and their mobility was moderately reduced.

The amplitude of the aortic component, expressed as the ratio of the amplitude of the second sound to that of the first sound over the right 2nd intercostal space, was, on the average, 2.0 in patients with a normal second sound on auscultation and 3.7 in those with an accentuated second sound. The mean difference was highly significant ($P < 0.001$). In the 3 patients with additional MI, in whom the second sound appeared to be accentuated on auscultation, a pulmonary component could not be distinguished with certainty over the 2nd left intercostal space, and it was therefore difficult to decide in these cases whether an accentuated pulmonary component was present or not.

Only in the more severe grades of AI, III and IV was an apical *third sound* noted, and this was found most commonly (in about 3/4 of the cases) in the younger age group (< 45 years) of whom more than half had signs of free AI with a large total stroke volume and pronounced peripheral pulse phenomena. This was also reflected in the fact that a third sound was more common in $AI_{IV \geq}$ than in $AI_{IV > 1}$. The older age group included, among others, 2 patients with additional MI (Nos. 88 and 106), 1 patient with residuum of myocarditis (No. 50) and a 60-year old man (No 83) with a history of left ventricular failure and objective signs of reduced myocardial function.

A *fourth sound* of varying frequency was recorded over the apex in 5 patients. In 3 of these patients (Nos. 11, 50 and 106) a third sound was also heard. The heart volumes varied greatly in these 5 patients, from a minimum of 585 to a maximum of 955 ml/m² body surface area. The left ventricular end-diastolic pressure (LV_{ED}) was greatly elevated in 3 patients even at rest, and in a 4th patient it increased during the exercise test to pathologically high values. In the 5th patient (No. 11) a 43-year-old man, who had a normal LV_{ED} both at rest and during exercise and who had the least pronounced heart enlargement, the third sound was only heard when he lay on his left side.

An *early systolic click* over the base or over both the base and apex was noted in the milder and more severe grades of incompetence. Common to these patients, among other things, was the finding that all except 3 had a good functional capacity and were in function class I or II, also that they had a normal LV filling pressure. Two of the patients in function class III A and B had a history of left ventricular failure. In none of the patients was the ascending aorta aneurysmally dilated.

3. *Heart murmurs*

(*a*) *Systolic murmur. Ejection type.* Among 39 patients with a systolic ejection murmur of grade 2–3 over the aortic area, the murmur in 33 of them was spindle-shaped or of the decrescendo type and did not cover more than about the first 2/3 of systole, thus it was of the *increased flow type.* In the other 6 patients as well as in the 23 patients with a basal ejection murmur of grade 4–5 the murmur was diamond shaped, thus of the *stenotic type* with the amplitude maximum during the first half or middle of systole. The basal systolic murmur of the stenotic type was transmitted to the neck and was sometimes louder over the neck than over the base. A *systolic thrill* was also palpable in 23 patients over the 2nd right intercostal space and/or over the neck. Of these 29 patients with a systolic murmur over the base, resembling that in aortic stenosis, only one patient had a weakened 2nd sound over the 2nd right intercostal space. At angiocardiography no reduced mobility or calcification of the leaflets was observed. From the angiocardiograms in the other 28 patients the aortic leaflets were assessed to be slightly thickened in 13 patients and moderately thickened in 1 patient, and the mobility was slightly reduced in 7 patients and moderately reduced in 4 patients.

Only in one of these patients were minor calcifications observed.

Of these 29 patients with a *basal systolic murmur of the stenotic type* and AI grade IV only 9 showed a systolic pressure gradient on simultaneous measurement of the pressure over the aortic ostium (see under "Methods" in chapter V p. 62) In 8 of these 9 patients the gradient at a relatively high effective flow was lower than 20 mmHg, but in one patient it was higher The mean values ±S.E.M. for the systolic pressure gradient and the simultaneously measured effective cardiac output *in these 9 patients at rest* were 10.2±2.6 (range 1–26) mmHg and 5.1±0.5 (range 3.1–7.1) l/min, respectively. During exercise the systolic pressure gradient over the aortic ostium increased in 4 of the 9 patients, remained unchanged in 2, and decreased very slightly in 2 patients (in 1 case it was not recorded during exercise) In a further 5 patients a previously absent systolic pressure gradient appeared during exercise. Thus a total of 13 out of the 29 patients with a systolic murmur resembling that in aortic stenosis had a systolic pressure gradient over the aortic valve during exercise amounting to an average of 14.8±2.8 (range 1–35) mmHg at an effective mean flow of 11.4±1.0 (range 4.9–15.5) l/min. (The cardiac output value from 1 patient was uncertain and has therefore not been included.) Only 1 of these 13 patients had AI of grade III—all the others had grade IV One female patient (No. 27) with a systolic pressure gradient over the aortic ostium of 26 mmHg at rest and 23 mmHg during exercise at effective flows of 5.99 and 12.53 l/min, respectively showed physical signs of free pronounced AI of grade IV ($AI_{IV\ pl}$). The other 2 patients (Nos. 5 and 10) with a systolic pressure gradient of over 20 mmHg during exercise (35 and 25 mmHg respectively) at a high effective flow of 15.5 and 15.0 l/min and an effective stroke volume of 111 and 100 ml at the time of the measurement of the pressure gradient also had AI grade IV

Regurgitant type In 4 of the patients with AI grade IV (Nos 84 88, 89 and 106) a high-frequency pansystolic murmur of grade 3–4 was noted over the apex and could be heard clearly out to the left axilla, thus being of the type usually found in mitral incompetence this diagnosis was verified by angiocardiography A further patient (No 70) who only had a systolic murmur of grade 2, which did not cover the whole of systole and was not transmitted to the left axilla, was found at thoracic aortography to have a slight leakage of contrast medium also to the left atrium. Since all these patients had severe AI of grade IV with rapid and complete contrast filling of the left ventricle on injection of contrast medium into the ascending aorta, the regurgitation to the left ventricle could be evaluated from the thoracic aortography The uncertainty which might have been caused by interfering arrhythmias, which can appear on injection of contrast medium into the left ventricle, was thus eliminated. From the thoracic cineangiograms the mitral incompetence was assessed as mild in 4 cases and moderate in 1 case (No 84) (see also chapter on angiocardiographic examinations, p. 112).

In 11 additional patients a high-frequency pansystolic murmur of grade 3–4 was heard over the apex and was clearly transmitted to the left axilla—in 5 cases with unchanged strength and in the others slightly weakened. This murmur therefore also appeared to be of the mitral incompetence type (cf Maiers 1964) but in no case was any contrast leakage to the left atrium observed with certainty on retrograde angiocardiography—with injection of contrast medium into both the left ventricle and ascending aorta in 6 patients and into the aorta alone in 5 patients. In 4 of these patients the evaluation of the mitral incompetence was uncertain on account of ventricular extrasystoles provoked by injection of the contrast medium into the left ventricle but in these cases—all with AI grade IV—no leakage of contrast medium to the left atrium was seen at thoracic aortography

In a further 11 patients, who had a prolonged apical systolic murmur of grade 2–3 retrograde left ventricular angiography was performed for the exclusion of possible MI. In none of these patients did leakage of contrast medium to the left atrium occur

(*b*) *Diastolic murmur* It is evident from Table 10 that there is some tendency to an increasing *intensity* of the high-frequency diastolic murmur over the aortic area with increasing severity of AI. Thus 80% of the patients with AI grade IV had a diastolic murmur of grade 3 or higher but this murmur intensity was also found in some patients with the mild AI grades I and II among others in two young, gracile women.

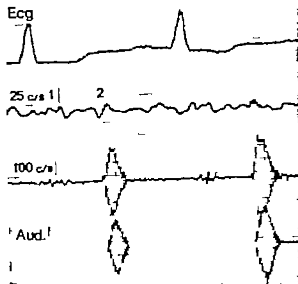


Fig. 4. Phonocardiogram and electrocardiogram of a 60-year old man with AI grade IV of unknown aetiology. PCG recording from the second right intercostal space at the sternal border. The amplification was 1/20. Filters with nominal frequencies of 25 and 100 c/s and one auditory filter were used. The paper speed was 100 mm/sec. A short musical diastolic murmur with a vibration frequency of 160 c/sec can be seen.

In all 81 patients the murmur was audible on auscultation with the patient supine, but in 1 patient (No. 50) with AI grade IV it was short and weak, of grade 1. It was this patient who had had myocarditis less than 1 year before admission to this hospital. In 2 patients (Nos. 98 and 100) with a pandiastolic murmur of grades 4 and 5, respectively, a diastolic thrill was felt, in the former case over the 3rd and 4th left and right intercostal spaces at the sternal borders, and in the latter case over the entire base and on the neck. Patient No. 98 had an aneurysmally dilated ascending aorta due to medionecrosis cystica, and a diastolic murmur had been discovered after a thoracic injury. He died of a dissecting aortic aneurysm. The other patient, No. 100, who had undergone a left-sided pneumonectomy, had AI of unknown origin with a murmur which had been detected 4 years previously. In both of these patients it was difficult to distinguish the second sound from the strong seagull-like murmur which in patient No. 98 was recorded phonocardiographically as a monofrequent sound-like accentuation lasting 10 csec, followed by a high-frequency diastolic decrescendo murmur. A similar pattern was recorded in the previously mentioned *60-year-old patient (No. 83) with AI grade III* of unknown origin and a clearly palpable second sound over the 2nd right intercostal space. Figure 4 shows a PCG recording from the latter patient with a monofrequent 8 csec broad musical murmur in the form of an accentuated sound-like pattern at the position of the second sound. On auscultation this was heard as a whining murmur at the beginning of diastole. With higher amplification a high-frequency prolonged diastolic decrescendo murmur was recorded over the 2nd and 3rd right intercostal spaces at the sternal border. In patient No. 100 the PCG recording (see Fig. 5) showed the previously mentioned monofrequent "fence-shaped" diastolic murmur with an initial dominating frequency of about 120 c/sec and a terminal frequency of 90 c/sec; it had its maximum over the 2nd left intercostal space. The murmur first began a few csec after the second sound and had its amplitude maximum 8–10 csec after the start of the second sound.

In 4 patients a sound-like accentuation was noted in the PCG 8–10 csec after the start of the second sound, in the high-frequency diastolic AI murmur, in 4 patients over the apex and in 1 patient over the 3rd left intercostal space. In 3 patients the amplitude maximum of the murmur was noted in association with the sound-like accentuation.

Not unexpectedly in almost half of all cases the *point of maximal intensity of the diastolic murmur* was located over the 3rd and 4th left intercostal spaces. In all except one of the 8 patients with an aneurysmally dilated ascending aorta the maximal point of the murmur was found over the 1st and 2nd right intercostal spaces; the same finding was made in 10 other patients with a relatively wide ascending aorta (aortic valve annular diameter in systole more than 40 mm, see chapter VII on angiocardiographic examinations, p. 112). In several patients with a dilated ascending aorta, however, the maximal point of the murmur was found to the left of the sternum. It is worthy of observation that in patients with the milder AI grades I and II the diastolic murmur had its maximal intensity over the 2nd left intercostal space—in contrast to the patients with AI grades III and IV, in whom the maximal point was seldom located so high up to the left of the sternum.

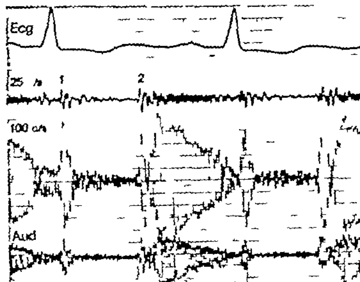


Fig. 5 Phonocardiogram and electrocardiogram of 57 year old man with AI grade IV of unknown aetiology and left-sided pneumonectomy. PCG recording from the second left intercostal space at the sternal border. The amplification was 1/50. Filters with nominal frequencies of 25 and 100 /sec and one auditory filter were used. The paper speed was 100 mm/sec. A musical diastolic crescendo-decrescendo murmur with vibration frequency of 120-90 /sec is seen.

With regard to the *transmission* of the murmur it may be mentioned that it was transmitted to the apex in 85% of the patients, to the left axilla in 61% to the jugular fossa in 50% and to the right axilla in 20%. In 3/4 of these latter patients with transmission of the murmur to the right axilla, the maximum point of the murmur was found over the 1st or 2nd right intercostal space. In the pneumonectomized patient (No. 100) with the strong musical murmur of grade 5 the murmur was transmitted both to the neck and the back. Five of the patients (Nos. 53 54 65 69 and 89) had a murmur of lower frequency over the apex in the middle and end of diastole with presystolic crescendo of the type usually referred to as the Austin Flint murmur. This will be discussed in more detail in chapter VI, p. 90.

Concerning the *duration* of the diastolic AI murmur this murmur as shown in Table 10 covered the whole of diastole in just over half of all patients with AI grades III and IV while a murmur of shorter duration was most common in the milder grades of AI.

Discussion

According to Grosse-Brockhoff and Loogen (1965) Strandell (1967) and Loogen et al. (1969) among others, it is not unusual in AI to find an *accentuated aortic component* in the second heart sound to which fibrotic changes of the valves and the rapid fall in pressure probably contribute (McKusick 1958). These authors also mention the occurrence of an early systolic click over the 2nd right intercostal space at the sternal border and apex, due to dilatation of the ascending aorta. The authors point out, however that these findings are most common in the mild grades of AI, while on the other hand a systolic click is rare and the second sound often weakened in severe AI, which is in essential agreement with the observations in the present series. Other authors, e.g. Holldack and Wolf (1958) have also drawn attention to the weakening of the second sound in severe AI. A *third sound* can be difficult to distinguish in AI but in those cases where it is noted it may be due to an increased filling rate at a large stroke volume or to impaired myocardial function. The *fourth sound* or atrial sound can be recorded and be audible in adults in the presence of increased resistance against left ventricular filling, as in decreased left ventricular compliance or an increased ventricular filling volume.

In patients with severe AI the characteristic diastolic murmur is often accompanied by a

strong *basal systolic murmur of the ejection type* with a thrill and radiation to the neck. This was noted as early as in 1832 by Corrigan. This com bined systo-diastolic murmur goes under the name "bellows murmur" (Friedberg 1966) McKusick pointed out in 1958 that this systolic murmur in AI need not be a sign of true stenosis of the aortic valves but may be due to the large stroke volume which together with the high velocity of systolic ejection of the left ventricle gives rise to increased turbulence in the dilated ascending aorta. This assumption of a flow-dependent systolic murmur in AI has been confirmed by Sare witz and Muehsam (1965) and Marquis et al. (1968) among others, who on catheterization of patients with AI and a systolic murmur suggestive of AS found no systolic pressure gradient over the aortic ostium. The systolic pressure gradient found in some of the patients with a basal systolic murmur in the present study was considered to be due to the large flow and not a sign of true AS.

In AI patients with a systolic murmur over both the base and the apex, it can be difficult to decide about the presence of *additional MI* solely from the quality of the apical systolic murmur and in such cases complementary information by angiocardiography is therefore required. As has been shown by Malers (1964) and other authors, there is in many cases good agreement between the angiocardiographically evaluated degree of severity of MI and the clinical findings, especially in isolated MI. The apical systolic murmur of MI type without angiocardiographically proved MI can probably be explained in most cases by transmission of the basal systolic mur mur to the apex. In some cases, however a slight regurgitant jet through the mitral orifice may ha e been overlooked at angiocardiography

One of the 5 patients with additional MI in the present series (No. 70) in whom the MI was judged from the angiocardiograms to be of a mild grade, differed from the other 4 patients as regards the nature of the systolic murmur this was only of grade 2, it did not cover the whole of systole and it was not transmitted to the left axilla—in other words there were no physically certain signs of MI. This patient had a low effec tive cardiac output of 3 2 l/min (cardiac index = 1 8 l/min per m²) and a low effective stroke volume of 45 ml, as well as signs of reduced LV function all of which can have contributed to reduction of the auscultatory impression of MI. In this connection it may be mentioned that in a few patients with mild grades of MI combined with MS especially in the presence of myocardial dysfunction, Malers (1964) only found an early systolic murmur of grade 1–3 with or without transmission to the left axilla.

Of the physical signs, the characteristic *high-frequency diastolic murmur* over the aortic area is the one which is decisive for the diagnosis of AI. It is usually described as a decrescendo mur mur beginning immediately after the second sound and gradually diminishing in intensity dur ing diastole. By means of PCG however several authors (Holldack and Wolf 1958 McKusick 1958 Watanabe and Sakamoto 1961 Dressler and Rubin 1966, among others) have observed in many cases a crescendo–decrescendo configuration with a short crescendo component after the second sound. Watanabe and Sakamoto (1961) found that the maximal amplitude of this crescendo–decrescendo murmur often coincided with the rapid filling of the left ventricle and the third sound, when the pressure difference over the aortic ostium was greatest. In severe AI the amplitude maximum was noted before the rapid filling period, how ever which was probably due to the large re gurgitation in this very first part of diastole.

The *sound-like accentuation* which in the PCG of 4 patients of the present series could be distinguished in the high-frequency diastolic murmur 8–10 csec after the start of the second sound was approximately concurrent with the opening of the mitral valves. This may correspond to what Luisada calls the opening sound" which be found in 8% of persons with no heart disease and in 18% of patients with an atrial septal defect (Luisada et al. 1949 Luisada and Argano 1971). In 3 of the patients this sound-like accentuation was followed by the amplitude maximum of the murmur which thus coincided with the be ginning of the rapid filling phase.

In rare cases the diastolic *AI murmur is musical* and often then goes under the name *sea-gull murmur*" (Gelfand and Bellet 1951 Groom and Boone 1955 McKusick 1958 Friedberg 1966) This was noted in 3 of the patients in the present study Characteristic of this form of murmur are loudness and extensive transmission, among other things. Gelfand and Bellet

Table 11 *Peripheral pulse signs in relation to AI grades III and IV*

		Number of patients AI grade						
			IV total				Total	
Peripheral sign		III	< 45 yrs	≥ 45 yrs	IV > Is	IV < Is	No.	%
Visible carotid	+	7	6	8	2	2	21	28
pulsations	+ +	1	18	16	8	12	35	47
Peripheral	+	3	5	6	2	1	14	19
pulses, palp	+ +	7	21	23	8	15	51	69
Capillary	+	5	11	9	5	4	25	34
pulsation	+ +	2	12	9	3	12	23	31
Femoral	+	3	7	12	6	4	22	30
art. sound	+ +	2	18	11	3	10	31	42
Pulsus click		1	18	9	6	12	28	38
Total number of patients		15	29	30	13	17		

Visible carotid pulsations: + moderately increased + + markedly increased.
Palp. peripheral pulses + moderately increased, + + pulsus celer et magnus.
Capillary pulsation. + apparent on finger nail pressure; + + spontaneous.
Femoral art. sound. + moderate strong; + + pistol shot sound

(1951) and Groom and Boone (1955), among others, have shown in PCG recordings that the musical AI murmur consists of pure sinus-shaped oscillations with a frequency of 90–340 c/sec: this was also observed in the 3 patients mentioned above. It has been considered that the regurgitating blood flow initiates vibration of an aortic valve with different types of deformity e.g. retroversion of a cusp, often the right anterior rupture of a cusp spontaneously or through trauma or perforation in subacute bacterial endocarditis (Gelfand and Bellet 1951 Groom and Boone 1955). Dressler and Rubin (1966) made a thorough PCG study of the variable contour of the musical murmur in AI and distinguished up to 3 successive peaks, of which the last was localized in the presystolic period.

In pure AI the *duration of the diastolic murmur* (Friedberg 1966) and its *intensity* (Stapleton and Harvey 1969) are related—(with some approximation)—to the degree of severity of the incompetence however in severe cases with congestive LV failure as well as in other conditions with a low cardiac output the murmur may be weakened and shortened (Watanabe and Sakamoto 1961 Grosse-Brockhoff and Loogen 1965 Loogen et al. 1969) Other factors that may also influence the loudness of the murmur include the transmission conditions, which are affected, among other things, by the configuration of the thoracic cage, emphysema, the direction of the regurgitant jet and variations in the peripheral vascular resistance. An increase in the peripheral vascular resistance can, as in hypertension, raise the diastolic pressure and thereby increase the intensity of the diastolic murmur, while a decrease of the peripheral resistance with an accompanying decrease of the diastolic pressure can reduce or abolish the diastolic murmur This has been observed by Marcus et al. (1970) in patients with aortic incompetence during pregnancy Experimental pharmacologically induced changes of the peripheral vascular resistance with ensuing changes of the diastolic AI murmur will be discussed in chapter VI, p. 89

This high-frequency diastolic regurgitant murmur which is usually more easily heard stethoscopically than recorded by PCG is probably the murmur that is most often overlooked, especially the short, weak variety of grade I It is an old experience that it is often heard best in expiratory apnoea with the patient sitting. The difficulty in hearing the diastolic murmur on auscultation in moderate AI combined with other valvular lesions is pointed out by Segal et al. (1964) in a report of 16 cases of so called silent AI confirmed by thoracic aortography

It is a general opinion that the diastolic murmur in AI is usually heard best at the left sternal border in the 3rd and 4th intercostal spaces

(McKusick 1958 Friedberg 1966, Wood 1968 Loogen et al. 1969). This finding was also made in 3/4 of the 801 cases of aortic incompetence reviewed by Sakamoto et al. (1968) thus in a considerably larger proportion than in the present series, where 47% had the maximal point of intensity at the location mentioned. The latter figure is probably an underestimation, as some of the patients in whom the murmur was heard with the same strength over the 2nd right and the 3rd left intercostal spaces (16%) could possibly have been included. In about 1/4 of the patients of the present study (27%) the maximal point of the diastolic murmur was located in the 1st or 2nd right intercostal space (in only 2 cases in the 1st right intercostal space) which is a considerably higher proportion than that reported by Sakamoto et al. in 1968 (7.1%). Most of the patients of the present series had a dilated ascending aorta, which was to be expected. These "right sided" diastolic murmurs are considered to have a special diagnostic value, since they mostly constitute signs of a dilated and rightwardly displaced aortic root and even an elongated aorta (Harvey et al. 1963 Sakamoto et al. 1968). The former authors mention the 3rd right intercostal space and also the 4th right intercostal space as a characteristic localization of the murmur in these right-sided" cases, while Sakamoto et al. (1968) found the maximal point in the 2nd right intercostal space in the majority of patients with right-sided" murmurs. In these cases elongation of the aorta was the dominating feature. The next most common localization was the 3rd right intercostal space. Only in 1 case was it localized in the 1st right intercostal space. In these patients with right-sided" murmurs the above authors also found marked LV enlargement, and it was considered that this in turn could contribute to rightward displacement of the ascending aorta.

II *Peripheral Signs*

1 *Peripheral pulse signs*

The *peripheral pulse signs* characteristic for patients with *AI* of *grades III and IV* are presented in Table 11 AI grade IV is divided both into the age groups below and above 45 years and into the sub-groups IV > 1s and IV < 1s. Of the total number of patients (81) 80% had some of the signs listed in the table. The percentage values given in the table refer to the 74 patients with AI grades III and IV Of these 9 patients had normal pulses, and these are not included in the table. Five of these 9 patients had AI grade III and 4 had grade IV All of these, with one exception, had a relatively low effective stroke volume of 49–72 ml at rest. One of the patients (No. 48) with AI grade IV and ankylosing spondylitis as well as osteogenesis imperfecta had a systolic pressure gradient over the aortic ostium of 18 mmHg at rest at an effective cardiac output of 5.7 l/min, but neither the auscultatory cardiac findings nor the angiocardiograms provided any evidence of true aortic stenosis. Another of these 9 patients (No. 81) had both a history of and haemodynamic signs of LV failure, and a third patient (No. 50) had residuum after a myocarditis.

As has been mentioned previously in this chapter the peripheral vascular signs in pure AI can diminish or disappear in the presence of a low blood flow and through vasoconstrictive influence with a resultant increased diastolic pressure (cf Gorlin and Goodale 1956, Stapleton and Harvey 1969).

The 7 patients with AI grades I and II all had normal pulses and are therefore not included in Table 11

About half of the patients with AI grade III had *pulsus celer et magnus*, while this finding was made in no fewer than 3/4 of the patients with AI grade IV All of these latter patients except 4 had palpable peripheral pulses which were stronger than normally The pulse characteristic of AI was noted in 88% of the patients with $AI_{IV<1s}$ and in 62% of those with $AI_{IV\ 1s}$. Thus in this series there was a tendency to an increasing frequency of peripheral vascular phenomena with advancing grades of incompetence (cf Grosse-Brockhoff and Loogen 1965 Friedberg 1966) A femoral arterial pistol shot" sound was found in 31 patients, and in 27 of them Duroziez's double femoral murmur could be heard on auscultation. Maximal peripheral signs (4 signs marked + + and with a palmar click) were found in 15 patients with AI grade IV (10 younger and 5 older than 45 years). In 11 of these it was possible to determine the total diastolic filling time of the left ventricle on the basis of thoracic aortography and of these patients 9 were in group $AI_{IV\ 1s}$.

Even though these peripheral signs are characteristic findings in AI, they are not pathognomonic for this disease and can occur in different conditions with hyperkinetic circulation and peripheral vascular dilatation. The *relationship between the palpatory pulse findings and* the directly and indirectly measured *pulse pressures* was studied. The direct systemic arterial pressure was measured in the aortic arch at the beginning of the heart catheterization (see methods, chapter V p. 62) and not simultaneously with the indirect brachial arterial pressure, which was measured a day or two earlier at the general physical examination. In blood pressure measurements with the cuff method the muffling of the Korotkov sounds was either undistinguishable or coincided with the disappearance of the sounds in 19 cases. The pulse pressure was calculated both from the level of muffling of the sounds and from the level of disappearance of the sounds. As can be seen in Table 12, a significant difference was found for all three variables between the group of patients with *pulsus celer et magnus* (C) and the group with normal peripheral pulses (A). Between the groups with moderately increased (B) and normal (A) pulses the difference was probably significant ($P < 0.05$) only for the indirect amplitude calculated from the disappearance level.

Table 12. *The palpatory signs of peripheral pulses in relation to direct and indirect systemic arterial pulse pressures in patients with AI grades III and IV*

		Arterial pulse pressure, mm Hg		
			Indirect brachial	
Peripheral pulses		Direct aortic	Muffling	Disappearance
A. Normal		9	5	9
	Mean	63	64	67
	S.D.	14.1	21.6	18.5
	S.E.M.	4.7	9.7	6.2
	C.L. 95%	53–74	37–91	53–81
B. Moderately increased +		14	9	14
	Mean	74	86	98
	S.D.	24.3	26.5	33.8
	S.E.M.	6.5	8.8	9.0
	C.L. 95%	60–88	66–106	79–117
C. Celer et magnus + +		48	41	51
	Mean	90	94	125
	S.D.	21.9	18.9	35.6
	S.E.M.	3.2	2.9	5.0
	C.L. 95	84–96	88–100	115–135
Differences B–A	P	>0.05	>0.05	<0.05
C–A	P	<0.001	<0.01	<0.001
C–B	P	<0.05	>0.05	<0.05

The disappearance column includes values down to zero.

Table 13. *Indirect brachial arterial pressure in relation to AI of varying degrees*

		Indirect blood pressure, mm Hg				
		Systolic	Diastolic		Pulse pressure	
AI grade			Muffling	Disappearance	Muffling	Disappearance
I		1	1	1	1	1
	Value	130		80		50
II		6	4	6	4	6
	Mean	129	75	70	53	59
	Range	115–145	65–90	50–90	40–70	40–90
III		15	7	15	7	15
	Mean	145	74	65	76	87
	S.D.	16.0	11.0	25.3	9.8	33.9
	S.E.M.	4.1	4.1	6.5	3.7	8.8
	C.L. 95	136–154	64–84	51–79	67–85	68–105
IV < 45 yrs		29	25	29	25	29
	Mean	148	56	20	91	129
	S.D.	20.7	11.3	29.0	24.3	37.0
	S.E.M.	3.9	2.3	5.4	4.9	6.9
	C.L. 95	140–156	52–61	9–31	81–101	115–143
IV ≥ 45 yrs		30	23	30	23	30
	Mean	160	67	46	93	114
	S.D.	23.9	13.4	32.2	21.0	36.5
	S.E.M.	4.4	2.8	5.9	4.4	6.7
	C.L. 95%	151–169	61–72	34–58	84–103	100–127
IV total		59	48	59	48	59
	Mean	154	61	33	92	121
	S.D.	23.0	13.2	33.1	22.5	37.2
	S.E.M.	3.0	1.9	4.3	3.3	4.8
	C.L. 95%	148–160	57–65	25–42	86–99	112–131

The disappearance columns include values down to zero for the following numbers of patients: 1 in AI_{III}, 19 in $AI_{IV} < 45$ yrs, and 9 in $AI_{IV} \geq 45$ yrs.

2. *Indirect blood pressure values*

Table 13 presents statistical values for the *systolic and diastolic pressures* and for the *blood pressure amplitude* on indirect measurement of the brachial arterial pressure in different grades of AI. Not unexpectedly it was found that with an increase of the grade of incompetence from the angiographically determined grades I and II to grade IV there was, on the average, a progressive

increase of the systolic pressure and of the blood pressure amplitude and a progressive decrease of the diastolic pressure but the limits were wide with overlapping between the groups. The difference between AI_{III} and AI_{II} was probably significant ($P < 0.05$) only for the systolic pressure. Between $AI_{IV\ total}$ and AI_{III} there was no significant difference in the systolic pressure but a significant difference was found for the diastolic pressure ($P < 0.001$ for disappearance and < 0.05 for muffling of the sound) and for the pulse pressure on calculation from the disappearance level ($P < 0.01$) included in the statistical calculation, however were 28 patients with diastolic pressure values as low as zero in group AI_{IV} and 1 in group AI_{III} When these patients were excluded from the calculation a non-significant mean difference between AI_{IV} and AI_{III} of -8.5 mmHg ($P < 0.05$) was obtained for the diastolic pressure at the disappearance level, but the difference in amplitude, which was 20 mmHg, was still significant ($P < 0.01$)

In the patients with AI_{IV} the older age group had probably significantly higher systolic pressures ($P < 0.05$) and a significantly higher diastolic pressure ($P < 0.01$) according to both measurement versions, on the other hand there was no significant difference in amplitude. Since 19 of the patients under 45 years of age had a disappearance value of zero as compared with only 9 in the older group a comparison was made in this case also after exclusion of the patients with disappearance of the sound at zero In this comparison a mean value ($\pm$S.E.M.) of 57 ± 5 mmHg ($n = 10$) was obtained for the diastolic pressure in the group younger than 45 years and 63 ± 4 mmHg ($n = 21$) for those 45 years and older The corresponding values for the amplitude were 86 ± 6 and 99 ± 4 mmHg: thus under these conditions the amplitude was somewhat higher in the older age group The difference was not significant either for the diastolic pressure or the amplitude (6 and 13 mmHg, respectively) It should be pointed out here that the evaluation of the pressure difference between these age groups is rendered difficult by the fact that arteriosclerosis and rigid vessel walls in older patients may give rise to an uncertainty factor in blood pressure measurement by the cuff method. Furthermore, in the older age group there were several patients with LV failure and probably increased peripheral vasoconstriction with an ensuing increase of the diastolic pressure.

Even though, as mentioned previously many factors can influence the level of the diastolic blood pressure, the diastolic pressure, in particular has been accepted by several authors as a simple clinical measure of the severity of the regurgitation (Watanabe and Sakamoto 1961 Friedberg 1966, Loogen et al. 1969 and others) The diastolic pressure at the level of muffling of the sound is often reported to lie at 50 mmHg or lower in severe AI. The magnitude of the blood pressure amplitude is also reported by these authors to run parallel with the grade of incompetence but a high amplitude is no proof of the presence of AI since the pulse pressure can be affected by many factors and may be due solely to an elevated systolic pressure when the diastolic pressure is normal or even raised. The high blood pressure amplitude in severe AI is due partly to the low diastolic pressure and partly to the often simultaneously raised systolic pressure.

3 *Systolic popliteo-brachial gradient*

Frank et al. (1965) found, on the other hand, that both the diastolic pressure level and the pulse pressure were poorly correlated to the grade of incompetence as evaluated by thoracic aortography They found more intimate relationships, however between the four different angiographically determined AI grades and *the systolic pressure gradient between the popliteal and the brachial artery* calculated from indirect blood pressure measurement they considered this to be the best clinical measure of the degree of incompetence. In AI_{IV} they found a systolic gradient of more than 60 mmHg between these two arteries. In AI_{I} as in normal cases, the gradient was less than 20 mmHg. Loewenberg (1940) distinguished between real and functional AI on the basis of the blood pressure difference between leg and arm. In real AI he found the pressure difference to be large but in functional AI there was practically no difference at all. This has been criticised by Kotte et al. (1944) among others. On comparing direct and indirect blood pressure values in the arms and legs of patients with AI among other conditions, they found approximately the same systolic arm pressures with the two methods, but in the legs with the indirect method

a higher systolic pressure than in the arms: they considered this latter finding to be due to uncertainty in determination of the leg pressure with the cuff method.

Park and Guntheroth (1970) studied 3–15-year old children with congenital heart disease and in a comparative determination of the blood pressure in the brachial and femoral arteries they also found that on indirect measurement the systolic pressure in the legs was 11 mmHg higher than in the arms, but that on direct measurement there was no significant difference in either the systolic or diastolic pressure, nor in the mean pressure. This is in agreement with the results obtained by Pascarelli and Bertrand (1965) on comparison of the blood pressure in the arms and legs in 50 *adult patients of ages 15–91 years without aortic* valve disease. Neither did these authors (1965) find any significant difference on direct measurement of the blood pressure in the arms and legs of patients with AI. Technical difficulties in indirect determination of the leg pressure as well as a cuff that is too narrow will often give falsely high values, as has been pointed out by Pascarelli and Bertrand (1965) and Park and Guntheroth (1970). These latter authors have also expressed their opinion that increased amplification of the systolic pressure in the popliteal fossa below the puncture site in the femoral artery might contribute to the difference between the directly and indirectly measured pressures in the leg.

The importance of a suitable breadth and length of the sphygmomanometer cuff for the arm and leg has long been discussed (Bordley et al. 1951 Ström and Werkö 1958 Simpson et al. 1965 Kirkendall et al. 1967 Cullhed et al. 1968 Geddes 1970) and these dimensions have been found to have considerable influence on the accuracy of the determinations. As seen in Table 14 on simultaneous *recording of the intra-arterial brachial and femoral pressures* in a polyethylene catheter and a grey Odman-Ledin catheter respectively (with regard to the different types of arterial catheters used, see chapter V p. 62) in patients with AI grade IV a significant difference was obtained both between the systolic and the diastolic pressures. On indirect successive blood pressure measurement in the arm–leg (–arm) significant differences were also obtained between the arm and leg pressures in the different AI

Table 14 *Differences between the femoral and brachial arterial pressures in AI_{IV}. Direct measurements, mm Hg*

	Systolic pressure	Diastolic pressure	Mean pressure
	18	18	18
$\bar{d}$	11.3	−3.2	−2.4
S.D	8.1	5.0	7.1
S.E.M.	1.9	1.2	1.7
P	<0.001	<0.01	>0.05

grades (using the rightside extremities for the comparison). (A check of the arm pressure after determination of the leg pressure showed that in 9 cases out of 10 no change from the original value *had occurred; the change amounted to an* increase of 10 mmHg in 1 of the 10 patients in whom this was checked.)

The mean *difference* (±S.E.M.) in the *indirectly measured systolic pressure between leg and arm* was (mmHg)

for AI_{II} 25 ± 4 (−7)
AI_{III} 37 ± 4 (−15)
AI_{IV} 47 ± 3 (n − 59)
AI_{IV} ... 50 ± 7 (n − 13)
AI_{IV-th} 58 ± 6 (n − 17)

The difference for the group AI_{I-II} was significant ($P < 0.01$) and for the other groups highly significant ($P < 0.001$).

These findings on indirect blood pressure measurement show relatively good agreement with those of Frank et al. (1965). In spite of the uncertainty in the indirect method of blood pressure determination, the indirectly measured popliteo-brachial pressure gradient—clearly exaggerating the directly measured pressure gradient—can give a rough differentiation of the severity of the regurgitation.

4 *Indirect diastolic blood pressure*

Controversial views have been expressed and opinions are still divided concerning the level at which the *indirectly measured diastolic blood pressure* should be considered most correct. Korotkov (1905 cf Ruskin 1956) claimed that disappearance of the sounds should be regarded as the index of intra-arterial diastolic pressure. A committee of the American Heart Association and the Cardiac Society of Great Britain and

Ireland (1939) considered, however that the level of muffling of sounds was more correct. This level has also been accepted as the best index of diastolic pressure by Kirkendall et al. (1967) in another committee of the American Heart Association, but the importance of noting both the diastolic pressure values has been stressed. Even though the indirectly measured pressure is generally about 10 mm higher than the intra arterial pressure at the level of muffling, these authors consider that the laws of physics associate the point of muffling with diastolic pressure They also claim that muffling of the sounds constitutes a more reliable index of diastolic pressure at a high flow in which condition the levels of muffling and disappearance are widely separated, with disappearance values considerably lower than those measured directly sometimes as low as zero. In 1951 another committee of the American Heart Association had concluded that the disappearance of sound was a better index, and that the level of muffling should only be used when the sound persisted down to zero. Ström and Werkö (1958) recommended, on behalf of the Swedish Cardiological Society that both the diastolic pressure levels should be noted, and that if only one pressure is given it should be that corresponding to the disappearance of sounds.

In *comparative studies of directly and indirectly measured brachial arterial pressures* several authors have found that muffling of the sounds is a more precise index of the diastolic pressure both in children and adults (Roberts et al. 1953 van Bergen et al. 1954 Moss and Adams 1963) On the other hand London and London (1967) found in simultaneous measurements on the same artery an overestimate of the directly measured diastolic pressure by as much as 12–20 mmHg at the level of muffling and 4–10 mmHg at the level of disappearance. In two cases of AI, however the disappearance of sound recorded with the cuff method was only 2–3 mmHg above the directly measured diastolic pressures. On simultaneous pressure measurement in both arms, both Karlefors et al. (1966) and Forsberg et al. (1970) found good average agreement between directly and indirectly measured systolic pressures. There was a fairly large discrepancy between the directly and indirectly measured diastolic pressures at the disappearance of sounds. These authors found that the pressure obtained with the cuff method was 11 3–15 mmHg higher than that measured intra-arterially Forsberg et al. (1970) observed no systematic difference in blood pressure between the two arms with either of the methods.

Taussig and Cook (1913) found in clinical investigations that the auscultatory cuff method could be used just as well in AI as in any other condition and that the point of muffling of the sound was the best index for indirect determination of the diastolic pressure level, this has also been pointed out later by Loogen et al. (1969). Ragan and Bordley (1941) and Kotte et al. (1944) who made comparative studies of directly and indirectly measured diastolic pressures at the level of muffling in patients with aortic incompetence, pointed out, on the other hand, the uncertainty of evaluation of the diastolic pressure by the cuff method in AI According to Kotte et al. (1944) the error of the diastolic pressure measured by the cuff method averaged +24% in patients with AI as compared with +9% in normotensive and hypertensive subjects.

Fig. 6 shows the *relationship between the directly and indirectly measured diastolic pressures* in the present series of patients. The indirect brachial arterial pressure was noted both at the level of muffling and at the level of disappearance. In 10 of the patients with AI_{IV} the points of muffling and disappearance of the sounds could not be distinguished, and in 2 of them (Nos. 94 and 104) the sound was heard down to zero. Altogether 25 of the patients included in Fig. 6 (1 with AI_{III} and 24 with AI_{IV}) had a diastolic sound audible down to a cuff pressure of zero As mentioned previously both pressures were not measured simultaneously—the intra-arterial pressure was recorded from the aortic arch at the start of the heart catheterization and the brachial arterial pressure was measured a day or two earlier at the general physical examination. The comparison was nevertheless considered justifiable as the basal state was not so different at the time of the two examinations that it could be considered to have affected the diastolic pressure level to any appreciable extent. For all AI grades the mean value for the diastolic pressure at the point of muffling of the sounds was higher and at the point of disappearance lower than that for the directly measured diastolic pressure. The mean difference between the indirectly and direct

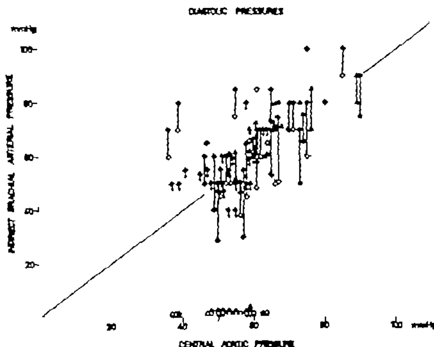


Fig. 6. Relationship between the directly measured central aortic pressure and the indirectly measured brachial arterial pressure in patients with AI grades I–IV. The indirect arterial pressure is given both at the points of muffling and disappearance of sounds.

Circles = AI_{I-II}; triangles = AI_{III}; diamonds = AI_{IV}.

Filled symbols = the point of muffling of the sounds. Open symbols = the point of disappearance of the sounds. These two points are joined by vertical line, except in those cases where the sound was heard down to cuff pressure of zero. In these cases the line is replaced by small arrow (see text p. 48 for further details). The line drawn is the line of identity.

ly measured diastolic pressures (±S.E.M.) for the value at the point of muffling was 0.5 ± 1.7 in AI_{I-II} ($n = 4$), 6 ± 3 in AI_{III} ($n = 7$) and 6 ± 1 mmHg in AI_{IV} ($n = 46$). The mean difference at the level of disappearance of the sounds was -9 ± 4 in AI_{I-II} ($n = 7$), -5 ± 5 in AI_{III} ($n = 15$) and -23 ± 3 mmHg in AI_{IV} ($n = 56$). Thus the differences at both the diastolic pressure levels were significant in AI_{IV} ($P < 0.001$). When the patients with a cuff pressure as low as zero at the level of disappearance of the sounds were not included, the difference for AI_{IV} at this level was no longer significant ($\bar{d} \pm$ S.E.M. -0.2 ± 2.5).

Even if no definite conclusions can be drawn with certainty from these comparisons between pressures that have not been recorded simultaneously, the muffling of the sounds seems to give the most reliable values both as regards pressure level and scatter in all grades of AI. This is in agreement with the experience of other authors in conditions of hyperkinetic circulation, discussed previously.

5. *Comparison between central and peripheral arterial pressures*

It is well known that the peripheral arterial pressure in systole is higher and in diastole somewhat lower than the central pressure (Rushmer 1961, among others), and that this finding is more obvious in AI (Wiggers 1931, Gordon et al. 1961, Ruttishauser et al. 1962, Loogen et al. 1969). Among other authors, Ruttishauser et al. (1962) has found that the more pronounced the regurgitation the greater the pressure difference between central and peripheral arteries.

As described in the foregoing, in the present study the indirectly measured peripheral arterial pressure was compared with the pressure measured directly in the aortic arch. In addition, however, the *relationship* was studied between the *directly measured pressures in the brachial artery and the aortic arch* (Fig. 7). This was done in 21 cases: 17 patients with AI_{IV}, 2 with AI_{III}, 1 with AI_{II} and 1 with AI_{I}. The statistical calculations were based on values from the 19 patients with AI

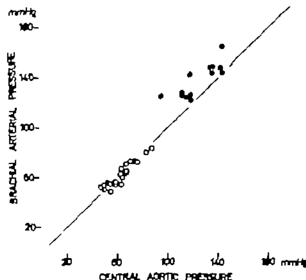


Fig 7 Relationship between directly measured central aortic pressure and brachial arterial pressur in 21 patients with AI of varying degrees: grade IV 17 grade III 2, grade II 1 and grade I 1 patient.

Filled symbols = systolic pressure. Open symbols = diastolic pressure. The line drawn is the line of identity

grades III and IV In 13 of these patients pressures were recorded continuously during withdrawal of a polyethylene catheter (PE 160) from the aortic arch to the brachial artery and in the other 6 patients pressures were recorded simultaneously via a PE 160 catheter in the brachial artery and a grey Ödman-Ledin catheter in the aortic arch. A non-significant mean difference of 1 4 mmHg ($P > 0\ 05$) was obtained between the diastolic pressure in the aorta and brachial artery while the systolic pressure values in the brachial artery were significantly higher than in the aorta ($P < 0.001$) with a mean difference of 15 1 mmHg. In the 13 patients whose recordings were made via the same catheter and with the same receptor and electromanometer the difference in diastole was somewhat higher viz. 1 9 mmHg, but still not significant. An intimate relationship was found between the two variables. When the calculations were made for all 19 patients with different catheters the correlation coefficient (r) for the systolic pressure was +0 88 (C.L. 95% 0.69–0.96) and for the diastolic +0.95 (C.L. 95% 0.86–0 98) for the 13 patients with only one catheter the correlation coefficient (r) for the systolic pressure was +0 86 (C.L 95% 0.54–0.96) and for the diastolic +0 97 (C.L. 95% 0.89–0.99)

It is evident from the above that the comparison made between the diastolic pressures measured directly in the aorta and indirectly in the brachial artery can be considered justified (cf also Loogen et al. 1969)

ELECTROCARDIOGRAM AT REST AND DURING EXERCISE

I *ECG at Rest*

In order to achieve as uniform as possible an evaluation of the patients' electrocardiograms (ECG) at rest it is desirable that these should be recorded under as similar conditions as possible. For this purpose, that ECG was chosen that was taken immediately prior to recording of the phonocardiogram and the subsequent exercise test, which examinations were performed at a de fined time point, on the day after admission of the patient to hospital and before the heart catheterization with angiocardiography

It has been claimed by several authors (Loogen 1965 Friedberg 1966, Tambe and Zimmerman 1967 Loogen et al. 1969 Spagnuolo et al. 1971) that in aortic incompetence there is a relatively intimate relationship between the degree of severity of the valvular lesion and the degree of ECG changes, especially in the form of conduction abnormalities such as left ventricular bundle branch block atrioventricular block of varying degrees and left ventricular hypertrophy

1 *Rhythm*

All patients except two in this series, including the 5 patients with mitral incompetence had sinus rhythm. The exceptions were 2 male patients aged 59 and 62 years (Nos. 99 and 85) with AI grades IV and III respectively of whom the former had atrial fibrillation with a normal ventricular frequency and the latter an implanted fixed-rate pacemaker with a frequency of 70 on account of episodes of A V block of varying degrees (I–III) Both of these patients had a history of left ventricular failure and considerable cardiac enlargement with relative volumes of 770 and 830 ml/m² body surface area. The aetiology of the valvular disease was unknown in the former patient. In the latter patient the ascending aorta was aneurysmally dilated (senile dilatation) and

this was assumed to be the cause of the valvular incompetence.

Discussion. In the absence of additional mitral valve disease the occurrence of atrial fibrillation is uncommon in aortic incompetence, and according to Loogen et al. (1969) and other authors it should arouse suspicion of concomitant myocardial failure. Myler and Sanders (1968) who have also pointed out the rarity of atrial fibrillation in pure aortic valve disease, have claimed that the development of this arrhythmia constitutes just as poor a prognostic sign as left ventricular failure in this type of valvular disease.

2. *Atrioventricular conduction*

In Table 16 (see p. 54) the *atrioventricular (A V) conduction times* are presented *with respect to degree of AI and digitalis therapy* In the following the group with digitalis will include 4 patients taking quinidine in combination with digitalis (Nos. 28 51 89 and 110) and one patient taking quinidine alone (No. 17). Since the P R interval was not corrected with regard to the heart rate, 20 csec was chosen as the upper normal limit, which is generally accepted for persons over 15 years of age (Savilahti 1946, Herbert 1970 among others).

Altogether 80 % of the patients had a normal conduction time of 20 csec or less, regardless of whether or not they were having digitalis therapy The mean value for the P-R interval for the 5 patients with AI grades I and II without digitalis was 16 csec and for the patients with AI grades III and IV with and without digitalis 18 and 17 csec, respectively The mean heart rates for the corresponding 3 groups were 68 67 and 67 beats/min In the only patient without digitalis with a prolonged A V conduction time this value was 22 csec at a heart rate of 60 beats/min. One third of the patients with digitalis therapy had a prolonged A V conduction time for such patients with AI grades III and IV the mean value was 24 (range 2_–32) csec at a mean heart rate of 70 (range 60–90) beats/min, while for the remaining patient, with AI grade II, the value was 24 csec at heart rate of 50 No significant difference was found between digitalized patients with normal and prolonged conduction times concerning left entricular end-diastolic pressure or end-diastolic olume, nor concerning total heart volume The very small difference with respect to the three latter parameters may perhaps be explained by the fact that the patients in the two compared groups were having digitalis therapy which means that in the large majority of cases the valvular disease was probably in a fairly advanced stage in both groups. Of the 8 patients with sinus rhythm and a history of left ventricular failure in this series, 4 had a prolonged A V conduction time Of the remainder 3 had a conduction time of 20 csec at heart rates of 80–90 beats/min.

Discussion. According to several authors (Segal et al. 1956, Colvez et al. 1959 Gordon et al. 1961 Loogen et al. 1969 Herbert 1970 among others) a prolonged A V conduction time is found in the more advanced stages of incompetence. Colvez et al. (1959) found a relationship between a greatly elevated LV filling pressure and a prolonged A V conduction time in patients with severe AI.

In a comparative study between 10 patients with AI who were not receiving digitalis and 10 normal persons, with a normal heart rate in both groups, Herbert (1970) found a significantly longer P-R interval in the patients with AI despite the fact that 6 of them had an A V conduction time within the normal range at the generally accepted upper normal limit of 20 csec, which, however in comparison with the author's normal material must be regarded as relatively prolonged. By reason of this finding, Herbert and Sobol (1970) discuss normal limits for A V conduction times and lowering of the upper normal limit to 18 csec as being a more realistic figure, provided that bradycardia is not present

Conduction defects, especially those with a prolonged A V conduction time (A V block I) are usually reported as a common finding in ankylosing spondylitis associated with AI (Bernstein and Broch 1949 Clark et al. 1957 Zwaifler and Weintraub 1963 Hoffman and Leight 1965 Weed et al. 1966). Of the 3 patients with ankylosing spondylitis in this series, only one (No. 24) had a prolonged A V conduction time (32 csec): he was also having digitalis therapy

In chronic forms of complete heart block, fibrosis of the conducting tissues has been found to be common. At autopsy of elderly patients with a high-grade A V block of unknown origin,

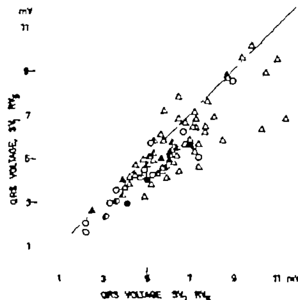


Fig. 8 Comparisons between the QRS voltages SV + RV and SV + RV (mV).

Circles indicate females, triangles males. The asterisk indicates a female patient with AI grade I. Filled symbols = AI grade II. Half-filled symbols = AI grade III. Open symbols = AI grade IV. The line drawn is the line of identity.

Bliss (1965) found mild functional AI due to senile dilatation of the aortic ring and in histopathological examinations observed fibrosis and sometimes calcification of the interventricular septum with ensuing compression or invasion of the underlying conducting tissue. The authors presented the theory that in patients with incompetent aortic val es a regurgitant jet may have produced these lesions of the interventricular septum.

3 *Ventricular compl xes*

QRS voltage. Figs. 8 and 9 show the relationships between different modes of expression of QRS voltage in the evaluation of possible left ven tricular hypertrophy viz. $SV_1 + RV_5$ *in relation to* $SV_2 + RV_5$, *and* QRS_{max}, respectively and the height of the QRS voltage in men and women with different grades of AI. As is evident from the figures, the oltage of the S wave in V_2 was in the majority of cases higher in some considerably higher than in V. The maximal QRS voltage among the leads V $_7$ was mostly lower than the sum SV + RV and thus even lower than the sum $SV_2 + RV_5$. On the basis of the mean values for the QRS amplitudes ($SV_1 + RV_5$ and $SV_2 + RV_5$) in the respective AI grades (2.2 and 2.6 mV respectively in grade I, 3.9 and 4 6 in grade II, 4 7 and 5 4 in grade III, 5.5 and 6.3 in pure AI_{IV} and 7 0 and 8 6 in AI_{IV} combined with MI) a successive increase of the QRS amplitude was found with increasing grades of incompetence but the range of distribution within the groups was wide, especially in AI grade IV with overlapping between the groups. The results arrived at in a comparison between the different AI grades are difficult to evaluate as the groups varied in size. With regard to $SV_2 + RV_5$, however it seems that there is a probably significant difference in amplitude ($P < 0.05$) between AI grades II and IV and between pure AI grade IV and grade IV combined with MI.

In Table 15 the *relationship between amplitude height* on the one hand, and *age VAT and ST T changes*, on the other was studied. It was found that just over half of the patients showed an amplitude between 4 and 6 mV and that 83% had a QRS voltage of 4 mV or higher With regard to the amplitude of the QRS complex in relation to different age groups, no tendency to a decrease in this amplitude with increasing age was found. Five male patients had a QRS ampli-

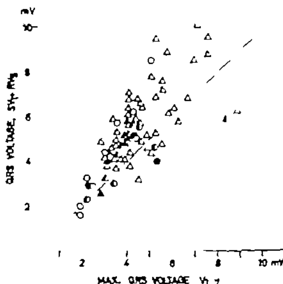


Fig. 9 Comparisons between the maximal QRS voltages (mV) among the precordial leads V_{1-7} and the QRS voltages SV + RV.

Circles indicate females, triangles males. The asterisk = female patient with AI grade I. Filled symbols = AI grade II. Half filled symbols = AI grade III. Open symbols = AI grade IV. The line drawn is the line of identity.

Table 15 *The sum of the voltages of SV_1 and RV_6 (mV) in relation to age, left ventricular activation time (VAT csec) and ST–T changes in left sided precordial leads in patients with and without digitalis therapy*

QRS voltage SV + RV mV	Number of patients Age groups, years 18–29	30–39	40–49	50–62	Total No.	Max VAT V V or VL Mean csec	Number of patients ST T changes in V and V: Slight, Without digitalis	Slight, With digitalis	Pronounced, Without digitalis	Pronounced, With digitalis
<3.5	3	4	3		10	4.2	1	1		
3.5–3.9	1	1	1	1	4	4.5				
4.0–4.4	1	1	6	4	12	5.0		3	1	3
4.5–4.9		5	3	3	11	5.0	1	2	1	3
5.0–5.4	2		4	4	10	5.3			2	2
5.5–5.9	3	2	4	1	10	5.6		3	1	
6.0–6.4	2	1	2	2	7	5.7			1	6
6.5–6.9	1	2		2	5	5.6			2	3
>7.0	3		3	5	11	6.0	1		1	8

ST T changes: slight = unspecific ST T changes with an S–T depression of 1 mm or less, in patients without digitalis flat and with digitalis negative T wave of unspecific type; pronounced = S–T depression of 2 mm or more and diphasic or negative T wave.
The group "with digitalis" includes 4 patients taking quinidine in combination with digitalis (3 patients with AI grade IV and 1 patient with AI grade II) and one patient taking quinidine alone (1 patient with AI grade III).
One male patient (No 85) with pacemaker is not included in the table.

tude higher than 10 mV and of these patients three were in the youngest age group while the other two were over 50 years of age and had concomitant mitral incompetence. One of these latter had the highest amplitude observed, viz. 11.4 mV. Further, with increasing QRS voltage there was slight, gradual prolongation of VAT with a highest value of 8 csec at an amplitude of 8.5 mV.

Left ventricular hypertrophy (LVH). In selecting the criteria for LVH, it was considered suitable, with the guidance of the data in Table 15, to place the amplitude criterion at 4 mV. Up to this amplitude level VAT lay below 5 csec and ST T changes of the type usually seen in LVH were only observed at QRS amplitudes above 4 mV. As shown in Table 16, the patients were divided into *five groups with respect to the degree of LVH* assessed from the QRS amplitude, VAT and ST T changes. The following criteria were established for assignment to the different groups.

Typical I $SV_1+RV_6 \geq 4$ mV, VAT > 5 csec and pronounced ST T changes, which meant a depressed S-T segment with an upwardly convex form and negative T wave 2 mm deep or more.

Typical II SV + RV ≥ 4 mV, VAT = 5 csec and pronounced ST T changes.

Probable I SV_1+RV ≥ 4 mV, VAT > 5 csec and slight unspecific ST T changes with an S-T depression of 1 mm or less, in patients without digitalis a flat and with digitalis a negative T wave of unspecific type.

Probable II SV + RV_6 ≥ 4 mV, VAT = 5 csec and slight ST T changes.

Suspected. SV_1 + RV ≥ 4 mV and VAT > 5 csec.

That which distinguishes Typical I from Typical II and also Probable I from Probable II is the difference in the length of VAT. In LVH Typical I and II the ST T changes were so marked and so characteristic that the ECG pattern was considered typical for left ventricular hypertrophy even with digitalis therapy, which could not be said for Probable I and II.

Table 16 gives the *distribution of the different LVH groups with respect to grades of AI and digitalis therapy.* Of the 36 patients whose ECG fulfilled the criteria of typical LVH, 2/3 were over 45 years of age and 3/4 were on digitalis. Not unexpectedly the 5 patients with concomitant MI belonged to this group. The 2 patients who were assigned to the group with suspected LVH were two young men, 21 years old, in function class I with high QRS amplitudes and a VAT of 6 csec but no T wave changes.

Altogether 34 patients had a VAT of 5 csec

Table 16. *ECG at rest in 75 patients with isolated AI of varying degrees and 5 patients with predominant AI of grade IV combined with MI of a slight to moderate degree. The patients are divided into two groups with respect to digitalis therapy*

ECG	Number of patients A without digitalis I	II	III	IV <45 y	>45 y	Total	B with digitalis II	III	IV <45 y	>45 y	IV+MI	Total	Total No. A+B
LVH													
typical I			2	2	2	6			4	9	4	17	23
typical II			1		2	3		1	4	4	1	10	13
probable I				2		2	1	1	1			3	5
probable II			1			1		1	2	2		5	6
suspected				1		1			1			1	2
P–R interval													
≤20 csec	1	4	7	14	7	33	1	4	11	11	3	30	63
>20 csec			1			1	1	2	3	7	2	15	16
Normal	1	3	4	4		12				1		1	13
Borderline normal		1		4	2	7		1		2		3	10
Pathological (without LVH)				1	1	2	1	2	2	1		6	8

LVH = left ventricular hypertrophy: typical I = SV + RV > 4 mV, pronounced ST–T changes and VAT > 5 csec; typical II = the same but VAT = 5 csec; probable I = SV + RV > 4 mV, slight ST–T changes and VAT > 5 csec; probable II = the same but VAT = 5 csec; suspected = SV + RV > 4 mV and VAT > 5 csec.
The group "with digitalis" includes 4 patients taking quinidine in combination with digitalis (3 patients with AI grade IV and 1 patient with grade AI grade II), and one patient taking quinidine alone (1 patient with AI grade III).
One male patient (No. 85) with a pacemaker is not included in the table. One patient (No. 99) with atrial fibrillation is not included in the group of P–R intervals.

and of these 19 were taking digitalis and/or quinidine (2 of these patients had digitalis combined with quinidine and 1 quinidine alone). Thirty-one patients had a VAT of more than 5 csec and 20 of these were taking digitalis (2 of them both digitalis and quinidine).

4 *Further ECG findings*

As shown in Table 16, those patients who could not be assigned to any of the five LVH groups described above were divided into three groups according to the type of ECG finding, as follows:

Normal, i.e. ECG within the limits of normal variation (Sjöstrand 1967).

Borderline normal: with slight depression (less than 1 mm) and/or slight change in shape of the S-T segment of no definitely pathological implication, positive T wave.

Pathological (without LVH): with unspecific ST–T changes with or without digitalis.

No patient showed the pattern of bundle branch block.

Five of the 7 patients with the mild AI grades I and II had a normal or borderline normal ECG. The 2 other patients with AI grade II, 2 men 49 and 50 years old, who had a pathological ECG were taking digitalis and digitalis plus quinidine, respectively, which medication would certainly have contributed to the pathological ECG pattern with ST–T changes. Nineteen (26%) of all patients with AI grades III and IV had a normal or borderline normal ECG.

5 *End-diastolic volume and wall thickness of left ventricle in patients with and without LVH*

In the patients with AI grades III and IV the mean values for the end-diastolic volume (EDV) and wall thickness of the left ventricle were calculated for the following 4 groups, which were formed by the combination of different groups included in Table 16: group 1 (normal group) = normal + borderline normal, group = LVH probable I + II + suspected, group 3 = LVH typical I + II and group 4 = all LVH groups (group

2 + 3) The following mean values were obtained for EDV (mean ± S.E.M.) for group 1 ($n = 12$) 375 ± 27 ml, group 2 ($n = 12$) 502 ± 37 ml, group 3 ($n = 22$) 627 ± 39 ml, and group 4 ($n = 34$) 583 ± 30 ml. *The corresponding values for the* thickness of the left ventricular wall were: group 1 ($n = 15$) 10.5 ± 0.5 mm, group 2 ($n = 10$) 11.3 ± 0.3 mm, group 3 ($n = 30$) 13.1 ± 0.5 mm and group 4 ($n = 40$) 12.7 ± 0.4 mm. On comparison between, on the one hand, *group 1 (normal + borderline normal)* and, on the other hand, group 3 (LVH typical I + II) and group 4 (all LVH groups) respectively significant differences were *found in both cases both for EDV ($P < 0.001$) and for the thickness of the left ventricular wall* ($P < 0.01$): the mean differences ($\bar{d} \pm$ S.E.M.) were 252 ± 48 and 208 ± 41 ml for EDV and 2.7 ± 0.7 and 2.2 ± 0.6 mm for left ventricular wall thickness, respectively. Between groups 1 and 2 a probably significant mean difference of 127 ml was found for EDV ($P < 0.05$) while the difference in wall thickness was not significant.

Discussion. In the *mild grades of AI* as well as in the *early stage of* more pronounced valvular incompetence a normal ECG is not seldom found (Lepeschkin 1951, Tambe and Zimmerman 1967, Loogen et al. 1969, Linhart 1971). On the other hand, ECG changes *indicating* left ventricular hypertrophy with S-T depression and inverted T waves, are often seen in the *more pronounced* grades of *AI* with a large EDV and during the late stages of the disease, when *secondary myocardial dysfunction* is often present in addition (cf. Loogen 1965, Friedberg 1966, Loogen et al. 1969).

In a comparative study of the function of the normal left ventricle as against the left ventricle that has been subjected to different kinds of pathological loading, Grant et al. (1965) found an increase in the *wall thickness* in patients with *chronic volume overload*: this increase was proportional to the chamber enlargement. In comparison with patients with a normal ECG, signs of a slight increase in the left ventricular wall thickness were also found in the present study in patients with an increased EDV and electrocardiographic signs of LVH.

In 1952 Cabrera and Monroy proposed the theory that there may be a difference in the *ECG pattern* between *systolic and diastolic overloading* of the ventricles, in the form, among other things, of high positive T waves in left precordial leads in volume overload of the left ventricle in contrast to S-T depression and negative T waves in cases with left ventricular pressure overload. *Other authors, however, for example* Selzer et al. (1962) and Braun (1965) found no such differences. Neither was any tendency to high positive T waves in the left precordial leads evident in the present series of patients with AI, but on the contrary abnormal, negative T waves especially in the more advanced cases of valvular incompetence with a high QRS amplitude (cf. Spagnuolo et al. 1971).

It is generally agreed that there is no satisfactory single criterion for LVH. Many different combinations of ECG criteria are found in the literature for diagnosis of left ventricular hypertrophy: of these the criteria proposed by Sokolow and Lyon (1949) *are among those most frequently* used. In a comparison between the angiocardiographically determined LV mass and the ECG *voltage criteria* for LVH used by Sokolow and Lyon (1949) and Grant (1957) respectively, Baxley et al. (1968) found that there was almost complete agreement in both cases, thus, 68 and 67% respectively of the 75 patients with anatomical LVH showed hypervoltage with the two *different* voltage *criteria.* The sum $SV_1 + RV_5 >$ 35 mm was given by Sokolow and Lyon (1949) as the voltage criterion. Some authors, on the other hand, have found it more appropriate to use *higher amplitude values in order to reduce* the number of falsely positive LVH cases. Thus, in comparative autopsy studies McPhie (1958) among others, found that the sum of max R + max $S > 45$ mm in the precordial leads gives a more accurate positive prediction than the sum $SV_1 + RV_5 > 35$ mm, and Skjaeggestad and Kjerulf (1969) observed that the best discriminating voltage criterion was max S + max R in $V_{1-6} >$ 40 mm, which was found in 85% in an LVH group and in 11% in a control group. In a study of the prognostic importance of different factors in AI, Spagnuolo et al. (1971) considered the sum $SV_1 + RV_5$ *to be abnormal only when it* was above 50 mm. Of the 36 patients regarded as having typical LVH in the present series, 32 fulfilled this criterion. As in the present series, *Hashimoto (1968) found in a cineangiographic* study of patients with mitral and aortic incompetence higher mean values for $SV_1 + RV_5$, the

more pronounced the grade of AI. In pure AI grade IV he found a high amplitude in all cases—higher than 7.8 mV

Included in the criteria of Sokolow and Lyon (1949) is $VAT > 5$ csec, which limit some authors have found to be too insensitive. In a comparative ECG and autopsy study Rosenfeld et al. (1962) found that prolongation of VAT beyond 5 csec only occurred in 7.4% of all cases of anatomical LVH. The corresponding figure was 25% in the patho-anatomical study of Skjaeggestad and Kjerulf (1969) but as high as 80% when they calculated from a VAT of 5 csec or more. Since this large increase in sensitivity only corresponded to a minor decrease in specificity (from 0–7% falsely positive cases) these authors considered it more appropriate to place VAT as 5 csec or more as a positive criterion for the LVH diagnosis.

Evaluation of the *ST T changes* in ECG assessment of LVH is rendered considerably more difficult and must be done with care in patients having digitalis (cf Nordström–Öhrberg 1964) and this also applies to quinidine. In this series of patients with AI it could be expected, as mentioned previously that more marked ECG changes would be found in the more severe forms of the valvular disease which also more often were treated with digitalis. It must be considered justifiable therefore, to attempt to assess the left ventricular hypertrophy from the ECG even in digitalis-treated patients, which was in fact possible with a relatively high degree of certainty in those cases designated as typical LVH, by studying the degree and nature of the ST T changes; in this series these differed clearly from changes due to digitalis alone.

Admittedly *digitalis* produces shortening (Scott et al. 1955 Sjöstrand 1967) and *quinidine* lengthening (Sjöstrand 1967 and others) of the *Q-T interval* but it was considered in the present study of LVH that the effect that digitalis and quinidine could be assumed to have on the activation time of the ventricle could be neglected. According to investigations by Rosenfeld et al. (196_) and others, the ventricular activation time as well as the QRS amplitude—in contrast to the ST T changes—maintained its specificity for LVH diagnosis despite digitalis therapy

II. *ECG Response to Exercise*

As shown in Table 17 the patients were divided into 5 groups according to their ECG response to exercise the table also includes 2 arrhythmia groups with different degrees of severity of the arrhythmia.

1 *Normal reaction*

Reaction within normal limits. Depression of S-T segment of less than 2 mm with or without flattening of the T wave during exercise with a gradual return within the first 4 minutes after work. The only patient having digitalis in this group had AI of grade III and only a slight change in shape of the S-T segment in the resting ECG (borderline normal) without increased ST T changes during exercise, and the ECG response was therefore regarded as normal.

2. *Elevation of the T wave*

Change of negative left precordial T wave (in three cases flat) at rest to positive during exercise, with gradual regression after exercise

In 7 of these 11 patients the T wave began to rise even in the sitting position on the bicycle ergometer before the start of the exercise (when the reference electrode was placed on the fore head) and during the actual work period further "normalization" took place. Seven patients showed at rest an ECG pattern that was classified as typical LVH, and two of them as probable LVH. In the 2 remaining patients with slight unspecific ST T changes and a VAT of 5 csec, the amplitude criterion of LVH was not fulfilled. One of the patients with this type of reaction (No. 50) had probably had myocarditis one year before the investigation at this hospital.

This type of ECG response during exercise with elevation of the T wave can be seen in patients with previous myocardial lesions and has been named *reaction as after previous myocardial lesion* This has been described by Lepeschkin (1951) Söderholm et al. (1962) Areskog and Hallén (1964) and Reindell et al. (1967a) in patients with ECG changes indicating previous myocardial infarction, by Thorén (1964) in cardiomyopathy in Friedreich's ataxia and by Petersson (1967) in patients treated surgically for atrial septal defect of the secundum type. Elevation during exercise of inverted T waves has been de

scribed by Boden and Bayer (1949 and 1950) and Lepeschkin (1951) in cases of aortic incompetence with left ventricular hypertrophy with ST T changes.

During exercise the heart rate is increased and diastole shortened with ensuing reduction of the regurgitant volume and increase of the mean aortic pressure in patients with AI. According to Boden and Bayer (1950) the elevation of the T waves during exercise in these patients may partly be attributed to resulting improvement of the coronary perfusion. The increased cardiac activity during exercise with subsequent coronary vasodilatation, may also contribute to an increased coronary circulation, but on the other hand it increases the oxygen consumption and the balance will hardly change except perhaps in localized areas. The normalization of pathological T waves during exercise can have other causes, however and may not necessarily be due to improved coronary circulation.

3 *Increased ST T changes*

Accentuation of ST T changes already present at rest, with ST T depression of 2 mm or more during work.

This type of reaction was the most common and occurred in just over half of all patients. About 3/4 of these patients were taking digitalis, which made it more difficult to evaluate the ECG changes during exercise and these could not therefore be attributed any definite pathological importance.

4 *Additional S-T d pression + negative T wave*

A normal or borderline normal ECG at rest in patients not taking digitalis, with the occurrence of S-T depression and a negative T wa during exercise and gradual regression after the exercise was ended The exercise thus meant *provocation* of the ECG pattern typical of *left ventricular hypertr phy* finding which has been reported previously by Brann (1965) among others.

5 *Pronounced S-T depression with a plateau and fter work a negative T wave*

During e ercise pronounced depression of the whole S-T segment by more than 2 mm—in 4 of the 5 patients more than 5 mm—with a plateau, and 4 min after exercise a deep negative T wave

Table 17 *ECG response to exercise in 79 patients with AI of varying degrees*

ECG reaction	Number of patients: II	III	IV: <45 y	IV: >45 y	Total: Without digitalis	Total: With digitalis
1 Normal	3	3	4	4	13	1
2. Elevation of the T-wave		1	2	8	4	7
3. Increased ST T changes	3	6	19	17	12	33
4 Additional ST depression + neg. T wa		2	1	1	4	
5 Pronounced ST depression with platea and after work neg T wave		2		3	2	3
6a. Arrhythmia I		3	3	1	5	
b. Arrhythmia II		1	1	5		7

Arrhythmia I high and increasing frequency of supraventricular extrasystoles and/or increasing frequency of monotopic ventricular extrasystoles during exercise.
Arrhythmia II heterotopic ventricular extrasystoles or runs of monotopic ventricular extrasystoles during and after exercise.
Two patients are not included one male patient (N 85) with pacemaker and one female patient (No. 105) with AI grade I, who had foot injury and was unable to carry out the exercise test.

with regression to the pattern at rest 10–20 min after exercise.

In all of these 5 patients the resting ECG showed signs of typical LVH, but despite this and despite digitalis therapy in 3 of the patients it was judged reasonable to interpret the ECG response to exercise to be pathological on the basis of the marked changes, which both in their nature and their time courses were typical of coronary insufficiency (cf Areskog and Hallén 1964)

During the exercise test 3 of the patients had subjective symptoms of angina pectoris at the time of recording of the plateau-shaped S-T depression. A fourth patient had a slight fall in blood pressure towards the end of the exercise test. The fifth patient, who had AI of syphilitic aetiology and history of subjective symptoms of angina pectoris, had no such symptoms during the xercise test, however despite the pathological ECG reaction.

more pronounced the grade of AI. In pure AI grade IV he found a high amplitude in all cases—higher than 7.8 mV.

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Change of negative left precordial T wave (in three cases flat) at rest to positive during exercise, with gradual regression after exercise.

In 7 of these 11 patients the T wave began to rise even in the sitting position on the bicycle ergometer before the start of the exercise (when the reference electrode was placed on the forehead) and during the actual work period further "normalization" took place. Seven patients showed at rest an ECG pattern that was classified as typical LVH, and two of them as probable LVH. In the 2 remaining patients with slight unspecific ST-T changes and a VAT of 5 csec, the amplitude criterion of LVH was not fulfilled. One of the patients with this type of reaction (No. 50) had probably had myocarditis one year before the investigation at this hospital.

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sion to the left axilla, which purely qualitatively was difficult to distinguish from a true MI murmur In a further 11 patients a prolonged apical systolic murmur of grade 2–3 was noted, which also resembled that in MI. In none of these 22 patients (27% of the series) however was any definite contrast leakage to the left atrium observed on angiocardiography These findings are also of importance from the aspect of differential diagnosis and thus as regards the indication for operation.

The *pulse phenomena* which are considered characteristic of AI were not found in AI grades I and II. In the more severe grades these phenomena were noted on the whole in increasing frequency with increasing severity of incompetence, and showed a fairly good relationship to the directly and indirectly measured pulse pressures. The indirectly measured *systolic popliteo-brachial gradient* also increased successively with increasing grade of incompetence this gradient, although in comparison with the absolute values it must be regarded as exaggerated, gives a rough but probably more differentiated idea of the severity of the regurgitation than the comparison of the directly measured pressures in the femoral and brachial arteries. Thus the mean difference in systolic pressure between the arm and leg was considerably higher with the standardized indirect than with the direct method of measurement.

With increasing grades of incompetence suc cessive increase in systolic pressure and blood pressure amplitude and a successive decrease in diastolic pressure were also seen, on the average but since the limits were wide no definite conclusions could be drawn concerning the individual case. Furthermore there is some uncertainty in blood pressure measurement by the indirect cuff method, by which completely misleading information may be obtained in isolated cases, with—especially in AI—falsely low diastolic pressure values at the level of disappearance of the sounds. In the present series the level of *muffling of the sounds* appeared to give the most reliable values in all grades of AI. In comparative (not simultaneous) studies of direct and indirect diastolic pressures, the average values for muffling of the sounds lay about 1–6 mmHg higher than the values obtained in direct intra-arterial measurement.

With increasing grades of incompetence there was a successive increase in the *QRS amplitude* with the highest amplitudes in the patients with $AI_{IV}+MI$ but the range of distribution was wide. In this series the group of ECG's designated *typical LVH*" also included ECG's from patients taking digitalis in those cases where the ST T changes were pronounced and deviated clearly from those due to digitalis alone. These patients could not be excluded despite the digitalis medication, since their disease was in an advanced stage, which is usually accompanied by LVH Patients with typical LVH according to their ECG were found to have significantly larger end-diastolic volumes and thicker left ventricular walls than the patients with a normal or borderline normal ECG Of the patients with palpable LVH about 2/3 had ECG changes as in typical LVH. In 4 of the patients with a normal ECG at rest and not taking digitalis, an ECG pattern of LVH was provoked during the exercise test.

V HAEMODYNAMIC FINDINGS

As mentioned in the previous chapter the diagnosis of AI can be made in the great majority of cases by clinical examination alone. For a rough evaluation of the degree of incompetence the blood pressure conditions usually give good guidance in patients with pure AI without decompensation. When a decision has to be made as to operation it may be necessary to complement the clinical examination with haemodynamic investigations in order to obtain more information on the degree of severity of the lesion and to exclude other concomitant cardiac disorders. A detailed haemodynamic evaluation can be obtained by flow determination and pressure measurements in both the right and left sides of the heart at rest and during exercise.

METHODS

General Aspects

Left heart catheterization in patients with AI

1 *Retrograde catheterization of the left ventricle* including pressure measurements and angiocardiography with contrast injection both into the left ventricle and into the ascending aorta, is the most informative single method in evaluation of the degree of severity of AI

A systematic catheterization of the left side of the heart was first performed in 1950 by Zimmerman et al with insertion of a catheter in the ulnar artery up to the ascending aorta. In patients with free AI they succeeded in introducing the catheter into the left ventricle In the same year Zimmerman reported that he had recorded the LV pressure in 10 patients with AI of these 7 were in congestive heart failure and had an increased LV diastolic pressure

2. *Transseptal left heart catheterization* which was originally described by Manfredi (1956) has had increasing application during the last decade It was Ross (1959 a and b) and Cope (1959) who first employed this method in animal experimental studies and in investigations in man. In 1960 Ross and co-workers gave a detailed description of the original transseptal technique Several investigators have since suggested modifications and improvements of the technique (Brockenbrough and Braunwald 1960 Bevegård et al. 1960 Gorlin et al. 1961 Bevegård et al. 1961 and 1963 Rainbow et al. 1967). This method which has had its greatest field of application in the examination of patients with aortic stenosis, can give important information on the pressure and flow conditions in patients with AI. In this way it is possible to assess both the systolic and diastolic pressure gradient across the aortic ostium at rest and during exercise. Further the method allows quantitative determination of the regurgitant volume by means of the dye dilution or thermal dilution method for example with sampling of the indicator in the left ventricle.

Different methods for determination of the regurgitant volume in AI

1 *Dye dilution methods* Several methods involving the dye dilution technique have been used in attempts to determine the degree of severity of the incompetence. Korner and Shillingford (1955 and 1956) analysed the *downstream dilution curve obtained after injection of the dye into the right atrium or the pulmonary artery* They found a flattened curve with a decreased peak concentration and marked disproportionate prolongation of the disappearance slope. The pathological curve form is obvious in severe incompetence but is not detected so easily in mild cases. A broad curve may also be obtained in patients with cardiac decompensation, but with proportionate prolongation of all time components (delayed appearance time delayed peak concentration and protracted disappearance slope) Thus in valvular incompetence with concomitant cardiac decompensation evaluation of the curve is rendered difficult or impossible. LaFarge et al. (1965) using a *fiber optic catheter* in the ascending aorta, were able

to determine the regurgitant volume with the dye dilution technique in 10 patients with AI and found good agreement with the regurgitant fraction determined from a combination of the angiographic and effective cardiac output estimations.

In 1958 Braunwald and Morrow described a practical *semi-quantitative method* with injection of indicator dye at different levels in the descending aorta for evaluation of the regurgitation. They determined the lowest point in the descending aorta from which the injected dye could be detected by oximetry at the right ear. This method has since been used by Rutishauser et al. (1962) and Aldridge (1962) among others. The latter author found an underestimation of the degree of incompetence in elderly patients and in patients with cardiac decompensation.

Salonikides et al. (1968) who recorded the curves from the left ear found that the results obtained with this dye dilution technique were highly comparable with the cineangiographic findings. A modified form of the method of Braunwald and Morrow was used by Warner and Toronto (1958) who instead of dye detection from the ear recorded dilution curves simultaneously from the left radial and femoral arteries.

A more sensitive method for determination of the regurgitant volume was described in 1958 by Guiddry and co-workers, who injected dye into the aorta above the valve and recorded dilution curves simultaneously from the left ventricle and a systemic artery (*the upstream sampling method*). In AI the maximal dye concentration appears earlier in the left ventricle than in the artery. Lacy et al. (1959) reported a method of calculation of the regurgitant flow in these cases by comparing the area below the dilution curves recorded proximally and distally to the incompetent valve. To obtain a quantitative measure of the degree of incompetence, Armelin et al. (1963, 1964) calculated the regurgitant fraction from the ratio between these curve areas in dog experiments. Bloomfield et al. (1966) gave a detailed account of the mode of calculation of the regurgitant fraction in patients with single and combined aortic and mitral valvular incompetence. Warner (1962) made a critical analysis of the method of quantitation of the regurgitation by sudden injection of indicator into the aorta, and pointed out the uncertainty of this method, in that the regurgitant volume is dependent upon where in diastole or systole the injection takes place. A better result is obtained if the injection time covers one or a few cardiac cycles (Bloomfield et al. 1966).

Frank et al. (1966 *a*) determined the regurgitant volume by the method of *continuous dye infusion* into the ascending aorta to avoid the uncertainty of the sudden injection technique with its poor reproducibility. The risk of erroneous evaluation of the grade of incompetence in cases of inconstant stroke volumes was thereby reduced. They found good correlation between the angiographically determined grade of incompetence and the regurgitant fraction determined by the method of continuous infusion ($r = +0.97$). It was this method that Stewart (1897) originally used for cardiac output determination. The continuous infusion curve can be constructed as the integral of a momentary injection (cf. Guyton 1963). The upper part of the curve has the character of a semilogarithmic function; this is of importance for the correction that is necessitated by recirculation.

2. *The thermodilution method* has been used by Krayenbühl et al. (1969) for quantitative determination of the regurgitation in patients with AI; they injected the indicator into the aortic root and recorded thermal dilution curves simultaneously from the left ventricle and the abdominal aorta.

3. *The isotope dilution method* with injection of radioactive tracers into the LV during diastole and external detection over the LV has been used by Hildner et al. (1969) among others, for quantitation of AI. The disadvantage of this method is that it does not allow differentiation between AI and MI.

4. *Electromagnetic flowmeters* have been used both in experimental studies on animals and in association with surgical operations in man for determination of the regurgitant volume in AI. Malooly et al. (1963) made a comparative study in the dog of the regurgitant fraction determinated simultaneously with a square-wave electromagnetic flowmeter and the previously mentioned upstream sampling dye-dilution technique for quantitation of AI. They found good correlation between these two methods ($= +0.91$). Several authors, among others Morrow et al. (1965)

V HAEMODYNAMIC FINDINGS

As mentioned in the previous chapter the diagnosis of AI can be made in the great majority of cases by clinical examination alone For a rough evaluation of the degree of incompetence the blood pressure conditions usually give good guidance in patients with pure AI without decompensation. When a decision has to be made as to operation it may be necessary to complement the clinical examination with haemodynamic investigations in order to obtain more information on the degree of severity of the lesion and to exclude other concomitant cardiac disorders. A detailed haemodynamic evaluation can be obtained by flow determination and pressure measurements in both the right and left sides of the heart at rest and during exercise

METHODS

General Aspects

Left heart catheterization in patients with AI

1 *Retrograde cathet rization of the left ventricle* including pressure measurements and angiocardiography with contrast injection both into the left ventricle and into the ascending aorta is the most informative single method in evaluation of the degree of severity of AI

A systematic catheterization of the left side of the heart was first performed in 1950 by Zimmerman et al with insertion of a catheter via the ulnar artery up to the ascending aorta. In patients with free AI they succeeded in introducing the catheter into the left ventricle. In the same year Zimmerman reported that he had recorded the LV pressure in 10 patients with AI of these 7 were in congestive heart failure and had an increased LV diastolic pressure.

2. *Transseptal left heart catheterization,* which was originally described by Manfredi (1956) has had increasing application during the last decade. It was Ross (1959 *a* and *b*) and Cope (1959) who first employed this method in animal experimental studies and in investigations in man In 1960 Ross and co-workers gave a detailed description of the original transseptal technique Several investigators have since suggested modifications and improvements of the technique (Brockenbrough and Braunwald 1960, Bevegård et al. 1960 Gorlin et al. 1961 Bevegård et al. 1961 and 1963 Rainbow et al. 1967) This method which has had its greatest field of application in the examination of patients with aortic stenosis, can give important information on the pressure and flow conditions in patients with AI In this way it is possible to assess both the systolic and diastolic pressure gradient across the aortic ostium at rest and during exercise. Further the method allows quantitative determination of the regurgitant volume by means of the dye dilution or thermal dilution method, for example with sampling of the indicator in the left ventricle.

Different methods for determination of the regurgitant volume in AI

1 *Dye dilution methods* Several methods involving the dye dilution technique have been used in attempts to determine the degree of severity of the incompetence. Korner and Shillingford (1955 and 1956) analysed the *downstream dilution curve* obtained after injection of the dye into the right atrium or the pulmonary artery They found a flattened curve with a decreased peak concentration and marked disproportionate prolongation of the disappearance slope. The pathological curve form is obvious in severe incompetence but is not detected so easily in mild cases. A broad curve may also be obtained in patients with cardiac decompensation but with proportionate prolongation of all time components (delayed appearance time delayed peak concentration and protracted disappearance slope) Thus in valvular incompetence with concomitant cardiac decompensation evaluation of the curve is rendered difficult or impossible LaFarge et al. (1965) using a *fiber optic catheter* in the ascending aorta, were able

was introduced into the right (in a very few cases the left) femoral artery by the percutaneous technique of Seldinger (1953) and advanced to the ascending aorta. In 23 patients the catheter was passed into the left ventricle retrogradely for LV angiocardiography and then witdrawn to the ascending aorta. The tip of the catheter was placed 1–2 cm above the aortic valvular plane Its position was checked by injection of a small test dose of contrast medium and the catheter was then fixed in position with adhesive plaster at tached to the skin. The regurgitant fraction was then determined by the continuous dye infusion method (Frank et al. 1966 *a*) in 19 patients at rest and in 6 patients during a second exercise test.

The right heart and the transseptal left heart catheterizations were performed by the author and the retrograde left heart catheterizations by a radiologist, as a rule L. Björk, M.D

2. *Cardiac output*

(a) The direct Fick principle Oxygen uptake and carbon dioxide elimination. The expired volume was measured with a gasometer (Nordgas, Stockholm Sweden) and the expired air analysed according to the Haldane method as modified by Enghoff (1946) The gas analyses were performed in duplicate and the error of a single determination in this laboratory was 0 02 volume per cent for O_2 and 0.01 volume per cent for CO_2. The values obtained for O uptake were compared with the normal values obtained from current tables (Harris and Benedict 1919)

Oxygen saturation and oxygen capacity The O saturation was determined by spectrophotometry of haemolysed whole blood (Holmgren and Pernow 1959 Karendal et al. 1968) The error of a single determination was 0.2 saturation per cent at an average O_2 saturation of about 75 % The *haemoglobin* concentration was determined spectrophotometrically after conversion to cyan methaemoglobin. The error of a single deter mination was 0 02 g % The *oxygen capacity* was determined from the Hb concentration under the assumption of an O binding capacity of 1.39 ml O_2 per g Hb (Ellers 1967 Sügbrand 1967). (In practice, this alue may vary slightly below the value 1.39 because of presence of inactive haemoglobins which are included in the Hb determination.) The *oxygen content* was calculated from the O_2 saturation and O_2 capacity values with the addition of physically dissolved O_2. The *arteriovenous oxygen difference* (AVD_{O_2}) is the difference in blood O content between a systemic artery and the pulmonary artery (If the O_2 binding capacity of Hb is lower than 1.39 the AVD_{O_2} becomes overestimated In many publications the earlier value of 1 34 is therefore still used, and average values of AVD_{O_2} in such materials will then be systematically lower by 3 6 %)

The error of a single determination calculated from 10 duplicate determinations of cardiac out put determined by the Fick method in this laboratory was 6.1 % (Wranne 1970).

(b) The dye dilution technique For measurement of the effective flow 5 mg of indiocyanine green in solution (Cardio-Green®) was injected into the pulmonary artery or right atrium and dye dilution curves were recorded by drawing blood at a constant rate from the arterial catheter through a Gilford model 103 (IR) Cuvette Densitometer with an amplifier and using a model 105-3 constant flow system. Duplicate determinations were made. The blood was kept sterile and reinfused to the patient after each cardiac output estimation. When the investigation was complete a five-point calibration curve was constructed from known concentrations of dye in blood samples from the patient. The dye dilution curves were calculated according to the con entional method of Kinsman and associates (1929) including manual semilogarithmic plotting, extra polation and planimetry of the curve area. The curve area as determined by this method with replotting was compared with a simplified proce dure which has been described by Pa ek and Karovič (1969) among others, in which the curve area was calculated without semilogarithmic plot ting and using a mathematical formula under the assumption that the downslope of the curve is a monoexponential function. There was good agreement between these modes of calculation (= + 0.999) even in cases with broad curves with a greatly prolonged disappearance slope the mean difference was 0.2 % ($n = 27$). The error of a single determination of cardiac output estimated by the dye dilution method obtained by calculation from duplicate determinations was 5 4 % both in the 31 cases in which the Fick method was used simultaneously and in 29 cases in-

Gilford Instrument Lab. Inc Oberlin, Ohio, U.S.A.

mediately prior to angiocardiographic examination for estimation of LV volumes. The mean difference (±S.E.M.) between the "Fick" and the "dye" values was 0.11±0.08 l/min, which meant that the "dye" value was on the average 2% lower than the "Fick" value.

For determination of the regurgitant flow with the *continuous dye infusion method* the effective flow was determined as described previously by the sudden injection of dye into, as a rule, the right atrium with sampling of blood from the central aorta or the brachial artery. Within 2–3 min afterwards, a dye solution containing Cardio-Green 1 mg/ml was infused at a constant rate of 30.7–31.0 ml/min through the grey Ödman-Ledin catheter which had been placed in position for the thoracic aortography. At a constant rate of about 30 ml/min blood was drawn from the transseptal catheter, which was placed with its tip in the mid-portion of the left ventricle between the outflow tract and the apex. The withdrawal of blood was continued until the indicator concentration in LV had reached an equilibrium, seen in the curve as a plateau, and a rise in the curve due to recirculation had followed. During the work test, for practical reasons the sampling of blood was done from the left ventricle even in determination of the effective flow and the interval between the measurements of the effective and regurgitant flows was only 1–2 min. When possible, duplicate determinations of both flows were made at rest and single determinations during exercise. A five-point calibration curve was constructed from known concentrations also for this continuous dye solution. The error of a single determination was 7.4% on calculation from 12 duplicate determinations of the regurgitant fraction expressed as regurgitant volume in per cent of the total stroke volume. The following formulae given by Frank et al. (1966 *a*) were used for calculating the regurgitant volume. The formula used for the effective (forward) flow on continuous dye infusion was:

$$\dot{Q}_f = \frac{\text{Indicator conc. infusion rate calibration factor}}{A_f}$$

where $\dot{Q}_f$ = the effective (forward) flow and A_f = the height of the plateau above the baseline of the arterial dilution curve. As the effective (forward) flow was determined by sudden dye injection and not by continuous infusion in the present series of patients, the area below the curve for the effective flow had to be recalculated for later calculation of the regurgitant flow. From the above equation it was possible to calculate the plateau height (A_f) that could be expected with continuous infusion at the prevailing effective flow determined by sudden injection. The regurgitant flow was calculated according to the following formula, which has been given by Levinson et al. (1959) for measurement of regional flow:

$$\dot{Q}_R = \frac{\dot{Q}_f}{(A_f/A) - 1}$$

where in the present cases $\dot{Q}_R$ = regurgitant flow, $\dot{Q}_f$ = effective forward flow, A_f = the height of the plateau above the baseline of the arterial dilution curve and A = the height of the plateau above the baseline of the left ventricular curve. This latter plateau, which was generally of 4–8 sec duration, represented a steady state when the indicator concentrations in LV and the aortic root were equal.

3. *Pressure measurements*

Pressures were measured with pressure transducers of the capacitance type (EMT 34 or 35[1]) connected to amplifier units and an electromanometer EMT 31.[1] The pressure curves and ECG were recorded on a direct-writing four channel or (since 1967) a six-channel ink jet recorder (Mingograf 42 and 81[1], respectively). The pressures were obtained by electrical integration. The paper speed was as a rule 25 mm/sec. End-*diastolic pressures were recorded with a paper* speed of 50 mm/sec and with a high sensitivity recording range—for LV_{ED} pressure an amplification corresponding to a full range of 50 mmHg. The reference level for zero pressures in the supine position was placed 5 cm dorsal to the sternal insertion of the 4th rib. Calibrations were performed with a water manometer before each investigation. The dynamic properties of the recording system used were about the same as were found by Cullhed (1964) on testing with a sine wave pressure oscillator. Recent testing of the dynamic characteristics of the catheter systems in this laboratory with the pressure step response

[1] Elema-Schönander Ltd., Stockholm, Sweden.

Table 18. *Intracardiac and central aortic pressures at rest in male and female patients with isolated AI of varying degrees and in five patients with AI grade IV combined with MI*

RA – right atrium, PA – pulmonary artery, LA – left atrium, LV – left ventricle, Ao – aorta, Ao_D–LV_{ED} gradient – the end-diastolic gradient over the aortic orifice (Ao_D – aortic diastolic pressure; LV_{ED} – left ventricular end-diastolic pressure)

Pressures, mmHg

AI grade		RA	PA			LA	LV		Ao			Ao_D LV_{ED} gradient
		M	S	D	M	M	S	ED	S	D	M	
I+II		4	4	4	4	4	4	4	3	3	3	3
♂	Mean	3	29	10	17	8	137	12	148	83	112	71
	Range	2–5	18–40	6–14	12–24	5–10	124–160	8–18	132–172	75–90	105–120	64–82
III		10	10	10	10	10	9	9	10	10	10	9
♂	Mean	3	34	14	22	8	146	16	154	74	108	59
	S.D.	2.1	12.3	6.8	9.6	4.3	17.4	7.9	17.4	9.3	12.9	11.6
	S.E.M.	0.7	3.8	2.2	3.0	1.4	5.8	2.6	5.5	2.9	4.1	3.9
IV<45		22	22	22	22	22	22	22	20	20	20	20
yrs	Mean	3	25	12	17	9	134	16	138	60	91	43
♂	S.D.	2.6	5.7	3.5	4.0	4.1	16.4	6.1	17.0	12.2	8.8	14.5
	S.E.M.	0.6	1.2	0.8	0.9	0.9	3.5	1.3	3.8	2.7	2.0	3.3
IV>45		22	22	22	22	22	17	17	22	22	22	17
yrs	Mean	2	33	14	21	11	164	17	161	64	101	52
♂	S.D.	1.4	15.1	7.5	9.9	6.3	31.6	7.9	77.9	14.9	19.4	15.9
	S.E.M.	0.3	3.2	1.6	2.1	1.3	7.7	1.9	5.9	3.1	4.1	3.8
IV+MI		5	5	5	5	5	4	4	5	5	5	4
♂+♀	Mean	2	51	24	35	24	158	22	153	59	95	36
	Range	1–4	43–68	19–32	27–46	17–33	117–178	19–24	114–185	50–64	90–112	27–40
I+II		3	3	3	3	3	3	3	3	3	3	3
♀	Mean	3	19	7	12	4	132	9	139	91	112	82
	Range	0–5	15–24	5–8	9–14	3–6	110–151	7–11	124–150	68–105	94–128	59–98
III		4	4	4	4	4	4	4	4	4	4	4
♀	Mean	3	20	7	13	5	136	7	139	73	103	65
	Range	1–4	15–23	4–9	10–16	4–6	110–156	4–13	130–154	60–95	95–117	54–82
IV 45		6	6	6	6	6	6	6	6	6	6	6
yrs ♀	Mean	3	27	13	18	9	151	14	148	58	94	44
	Range	0–6	17–42	6–23	12 79	3–11	112–190	4–29	116–189	42 73	76–105	25–58
IV>45		3	3	3	3	3	3	3	2	2	2	2
yrs ♀	Mean	4	33	16	23	11	153	17	163	57	98	37
	Range	3–5	19–54	13–26	14–36	6–21	146–158	11–28	158–168	45–68	93–102	17–57

method has shown a dynamic response of about the same magnitude or somewhat better for the catheters used in the present investigation. The transseptal teflon catheter had the same dynamic properties as the Ödman-Ledin catheter.

The *pulmonary vascular resistance* (PVR) was calculated as the ratio $(PA_M - LA_M)/CO$ and expressed in mmHg per l/min. PA_M = pulmonary arterial mean pressure. LA_M = left arterial mean pressure and CO = cardiac output. In a few cases (5 at rest and 3 during the exercise test) where the LA pressure was not recorded, the PCV pressure was used instead, wherewith the PCV value was converted to a corresponding approximate LA value by subtracting 2 mmHg from the PCV value at rest and 3 mmHg from the value during exercise. These figures comprise the rounded mean differences obtained on simultaneous recording of PCV and LA pressures in 23 patients at rest ($\bar{d} \pm$ S.E.M. = 1.5 ± 0.2 mmHg) and 15 patients during exercise ($\bar{d} \pm$ S.E.M. 2.6 ± 0.4 mmHg) all of whom are included in the present series. The *systemic vascular resistance* (SVR) was calculated as the ratio Ao_M/CO and expressed in mmHg per l/min, where Ao_M = central aortic mean pressure.

Table 19 *Intracardiac and central aortic pressures during exercise in male patients with isolated AI of varying degrees*

The values are given in relation to levels of exercise selected according to magnitude of O_2 uptake, ml/min (see text p. 67). RA = right atrium, PA = pulmonary artery LA = left atrium, LV = left ventricle, Ao = aorta, Ao–LV_{ED} gradient the end-diastolic gradient over the aortic orifice (Ao_D = aortic diastolic pressure; LV_{ED} = left ventricular end-diastolic pressure)

			Pressures, mmHg										
AI grade	$\dot{V}O_2$ at work		RA M	PA S	PA D	PA M	LA M	LV S	LV ED	Ao S	Ao D	Ao M	Ao_D–LV gradient
I + II	a			2	2	2	—		2	2	2	2	2
♂		Mean		37	14	25	—	168	8	175	98	125	90
		Range		34–39	14–14	24–25	—	155–180	6–10	165–185	95–100	125–125	89–90
	b			2	2	2	1	1	1	1	1	1	1
		Mean		36	17	24	15	165	10	167	100	128	90
		Range		28–44	14–19	20–28							
				3	3	3	3	3	3	3	3	3	3
		Mean		37	14	23	5	178	4	179	107	137	103
		Range		35–39	13–15	22 25	4–6	165–195	3–5	165–200	100–120	125–150	95–116
III				5	5	5	1	4	4	5	5	5	4
♂		Mean		63	29	42	35	195	28	185	95	133	68
		Range		36–92	16–46	4–69		184–207	10–50	160–199	83–118	120–150	46–84
	b		1	7	7	7	3	7	7	7	7	7	7
		Mean	0	46	20	31	13	184	18	199	99	140	81
		Range		32 58	12 23	20–36	3–20	145–214	6–35	172 229	84–116	122 161	54–101
				4	4	4	4	4	4	4	4	4	4
		Mean		47	21	32	9	194	15	201	103	145	88
		Range		44–50	19–23	29–35	3–16	183–214	7–29	185–226	95–115	131 150	66–103
IV 45				16	16	16	3	11	11	15	15	15	10
yrs		Mean		38	18	26	15	164	14	157	76	110	61
♂		S.D		8.9	5 7	6 0	3.5	28 1	5 9	23.3	5 8	9 7	10 6
		S.E.M.		2.2	1 4	1 5	2 0	8 5	1 8	6 0	1.5	2.5	3.3
	b		3	18	18	18	13	15	15	16	16	16	13
		Mean	3.3	40	18	28	12	171	11	168	79	117	67
		S.D.	1 5	14 8	8 9	11.0	9.5	29.9	6.1	20.7	9 9	8 8	11.5
		S E.M	0 9	3 5	2.1	2 6	2 6	7 7	1 6	5.2	2.5	2.2	3 2
			4	8	8	8	7	7	7	6	6	6	6
		Mean	–1 0	40	15	26	9	166	8	167	81	116	74
		S D	1.8	18 7	8 5	14.5	15 1	10.2	3.1	25 2	3 9	10 1	8.2
		S E.M.	0 9	6 6	3 0	5.2	5 7	3 9	1.2	10.3	1.6	4 1	3 4
V 45			1	14	14	14	8	11	11	13	13	13	11
yrs		Mean	2	56	27	37	16	191	18	190	83	125	71
♂		S.D		21 4	11 4	15 1	8 3	27 7	8 0	32.4	17 4	21 7	13 6
		S E.M.		5 7	3 0	4 0	2.9	8 4	4	9 0	4 8	6 0	4 1
	b		2	10	10	10	7	9	9	10	10	10	9
		Mean	2.5	48	20	32	14	209	15	204	89	138	77
		S.D	2 1	11.6	6 6	8.8	9 1	27 6	6.7	23 4	14 2	13 1	16 0
		S E M	1 5	3 7	2.1	2.8	3 7	9.2	2 2	7 4	4.5	4.2	5 3
			2	5	5	5	5	5	5	5	5	5	5
		Mean	0 0	48	18	30	13	233	12	219	97	143	85
		Range	1 1	35–65	11 30	20–49	4–77	144–280	5–25	148–255	74–124	100–173	69–115

4 *Basal metabolic rate*

A few days before the catheterization the basal O_2 uptake was measured by means of a Spirograph IV (Elema Schönander Ltd., Stockholm) under standardized conditions with duplicate determinations of 10 min duration each.

RESULTS

I. *Intracardiac and Intravascular Pressures*

The results of the pressure measurements at rest in men and women with different AI grades are presented in Table 18 and those during exercise in Tables 19 and 20. Since the sex difference was

Table 20 *Intracardiac and central aortic pressures during exercise in female patients with isolated AI of varying degrees and in five male and female patients with AI grade IV combined with MI*

The values are given in relation to levels of exercise selected according to magnitude of O_2 uptake, ml/min (see text p. 67).
RA = right atrium, PA = pulmonary artery LA = left atrium, LV = left ventricle, Ao = aorta, Ao–LV_{ED} gradient = the end-diastolic gradient over the aortic orifice (Ao_D = aortic diastolic pressure; LV_{ED} = left ventricular end-diastolic pressure)

			Pressures, mmHg										
AI grade	$\dot{V}O_2$ at work		RA M	PA S	PA D	PA M	LA M	LV S	LV ED	A S	A D	A M	Ao_D–LV_{ED} gradient
I + II				3	3	3	1	3	3	3	3	3	3
♀		Mean		29	13	21	6	150	6	157	103	123	97
		Range		25–33	11 18	18–23		135–165	6–6	152–160	92–114	115–13[illegible]	84–108
	b			2	2	2	2	2	2	2	2	2	2
		Mean		30	14	21	3	141	4	155	103	125	100
		Range		29–30	13–14	20–22	3–3	140–142	3–4	150–160	98–108	122 128	94–105
III	a		1	4	4	4	3	4	4	4	4	4	4
♀		Mean	5	32	14	23	8	163	9	154	91	116	83
		Range		29–39	12–15	21 25	6–11	138–168	7 11	150–159	89–101	95–123	68–93
	b												
		Mean		—	—	—	—	—	—	—	—	—	—
		Range											
IV < 45	a		2	6	6	6	4	6	6	7	7	7	6
yrs		Mean	3	38	20	27	14	193	19	179	80	119	63
♀		Range	0–5	22–55	8–40	13–46	3–32	146–228	8–41	134–215	68–94	96–142	32–86
	b			1	1	1	1	1		1	1	1	1
		Mean		30	14	21	7	150	10	154	89	116	79
		Range											
IV ≥ 45				3	3	3	1	3	3	2	2	2	2
yrs		Mean		52	28	39	39	197	24	212	88	145	60
♀		Range		35–80	16–46	25–60		178–220	16–39	195–229	86–89	136–154	47 73
	b			2	2	2	2	2	1	2	2	2	1
		Mean		39	20	28	15	186	19	194	89	137	77
		Range		34–44	16–24	23–33	10–20	173–198		182–205	82–96	130–144	
IV + MI				4	4	4	2	3	3	4	4	4	4
♂ + ♀		Mean		66	34	50	35	186	29	180	73	119	48
		Range		59–72	28–41	46–56	30–39	158–205	23–37	130–224	59–84	95–148	31 57
	b			4	4	4	4	2	2	4	4	4	2
		Mean		70	36	52	31	190	24	193	87	133	64
		Range		63–85	28–46	45–63	15–44	170–210	16–31	142–240	75–98	105–158	57–70

found to be small it was considered justified to combine the corresponding values for the evaluation of the pressure values. As regards the significance of the differences between the AI groups, reference may be made to Table 21.

Concerning the *values at rest* it was found that the mean pressure in RA lay within the normal limits, and that there was no significant difference between the different AI groups given in the table. The mean values for PA pressure lay essentially within the normal limits, but the values for group AI_{IV} + MI were elevated. Similarly it was this group that showed an elevated mean value for LA pressure. Concerning the systolic pressures in LV and the aorta, the highest values were obtained for group $AI_{IV} \geq 45$ years. The mean value for end-diastolic pressure in LV was normal in AI_{I-II} but slightly to moderately raised in the other groups, with the highest value in group AI_{IV} + MI. The diastolic aortic pressure showed a clear tendency to a successive decrease with increasing grades of AI. The same applied to the end-diastolic gradient over the aortic ostium.

Since the work loads used at the catheterizations varied within relatively wide limits, it was considered more appropriate to relate the *pressure values during exercise* to the O_2 uptake. For this

Table 21 *Significances of pressure differences between varying AI grades at rest and during exercise*
The alues indicate $P<$ For bbreviations see T bles 18–20.

AI degrees	RA M	PA S	PA D	PA M	LA M	LV S	LV ED	Ao S	Ao D	Ao M
I+II III										
Rest										
Work		0.10				0.10				
Work b										
I+II–IV<45 y										
Rest				0.05					0.001	0.001
Work									0.001	0.10
Work b									0.005	0.10
I+II–IV≥45 y										
Rest			0.10	0.05	0.10			0.10	0.001	
Work		0.025	0.025	0.025		0.02		0.05	0.05	
Work b		0.05		0.10		0.005		0.025	0.10	
I+II IV+MI										
Rest		0.05	0.001	0.001	0.001		0.01		0.005	
Work		0.001	0.001	0.001					0.005	
Work b		0.001	0.005			0.05			0.10	
III IV<45 y										
Rest									0.001	
Work									0.001	
Work b							0.05			
III–IV 45 y										
Rest									0.01	
Work							0.10	0.025		
Work b										
III IV MI										
Rest									0.02	
Work			0.10		0.01				0.02	
Work b							0.10			
IV<45 y IV 45 y										
Rest		0.01								
Work		0.001	0.025	0.05				0.005		
Work b						0.005		0.005	0.05	0.001
IV 45 y IV+MI										
Rest							0.10			
Work			0.005	0.001	0.05					
Work b			0.001		0.005		0.001			
IV≥45 y IV MI										
Rest										
Work					0.10					
Work b			0.001		0.02		0.025			

purpose a division into 3 groups, *a*, *b* and *c* was made. Group *a* comprised O_2 uptake alues of 500–1 000 ml, group *b* values of 1 000–1 500 ml and group *c* alues of 1 500–2 000 ml/min. The patients were thus placed in one or two of the groups depending upon whether they performed one or two work loads.

Of the 19 patients in whom the *RA pressure* was recorded during exercise a slight decrease was noted in 9 patients, a slight increase of a few mmHg in 5 and no change in the other 5 patients

The *LV filling pressure* has been given except for patients with MI as the mean pressure measured in LA which decreased during exercise (the highest performed work load) in 29 patients by an average of 38%. In AI_{III} $(n=25)$ it decreased by 37 ± 3.6 (mean $\pm$ S.E.M.)% and in AI_{II} $(n=4)$ by 45 ± 7%. The end-diastolic pressure in LV was also recorded, however and this decreased during exercise in 31 of the patients

Table 22. *Left atrial and left ventricular pressures in 5 patients with AI combined with MI*

LA = left atrium, LV_{ED} = left ventricular end-diastolic pressure

Patient No.	Rest LA Mean	Rest LA wave peak	Rest LA Diastole pre wave	Rest LA Diastole point	Rest LV_{ED} pre wave	Rest LV_{ED} post wave	Work LA Mean	Work LA wave peak	Work LA point	Work LV_{ED} post wave
70	21	28	19		15	23	39	56	30	28
84	33	48	27				23	37	20	
		41	16	22	14	23				
88	17	24	10	20	12	21	38	55	31	35
89	23	46	13	21	15	24	44	74	31	31
106	24	44	15		15	24	15	30	6	16

with AI_{III} by a similar value of $37 \pm 3.3\%$. Of the 29 patients with a decreasing LA pressure during exercise, 21 were relatively young, below 45 years of age.

In patients with AI_{II} the pressure reactions in both the right and left heart were essentially normal. In AI_{III-IV} the PA pressures were slightly to moderately elevated at the different work loads. On comparison between the change in the diastolic aortic pressure from resting conditions to exercise corresponding to work load *b* (an O_2 uptake between 1 000 and 1 500 ml) the following percentual increases were obtained for the different AI grades: 20% for AI_{II}, 25% for AI_{III}, 32% for $AI_{IV} < 45$ years and 39% for $AI_{IV} \geq 45$ years. There was a tendency even during exercise for a reduction of the diastolic aortic pressure to occur with increasing grades of AI.

A *systolic pressure gradient* over the *aortic ostium* was recorded on simultaneous measurement of the pressure in LV and the aortic arch in a total of 18 patients (15 with AI) at rest and in 28 patients (21 with AI_{IV}) during exercise. The mean values at rest $\pm$S.E.M. for the systolic pressure gradient and the simultaneously measured effective cardiac output and stroke volume were 7.7 ± 1.7 (range 1–26) mmHg, 5.1 ± 0.3 (range 3.1–6.7) l/min and 66 ± 4 (range 38–91) ml, respectively. During exercise the corresponding values were 12.8 ± 1.7 (range 1–35) mmHg, 11.4 ± 0.6 (range 6.1–16.8) l/min and 88 ± 5 (40–132) ml. At angiocardiography slightly thickened cusps with slightly reduced mobility were found in 8 of these patients, and moderately thickened cusps with moderately reduced mobility in 4 patients, but in no case were any signs of true anatomical stenosis observed. In 2 of these patients minor calcifications were seen on the angiocardiogram. A systolic pressure gradient of over 20 mmHg was noted in only 1 patient at rest (No. 27) and in 4 patients during exercise (Nos 5, 10, 27 and 39). All 4 patients showed physical signs of free, pronounced AI of grade IV. Three of these patients have been operated on, in 2 of them completely prolapsed cusps were found at operation, and in the third case (No. 39 with syphilitic AI) a dilated annulus and thin cusps, thus no signs of stenosis.

In Table 22 a detailed analysis has been made of the *pressure levels* in *LA* and *LV* at rest and during exercise in the 5 patients with AI_{IV} *combined with MI*. The pressures in the two cardiac chambers were measured in rapid sequence one after the other through the transseptal catheter. Only in patient 84 were the pressure measurements performed simultaneously and this was at rest immediately prior to retrograde left ventricular angiocardiography. As can be seen in the table and in Fig. 10, there was good agreement between the diastolic pressure in LA (PCV) and LV measured immediately before the *a* wave and the diastolic pressure measured at the onset of the isovolumetric LV contraction—designated *z* point pressure in the LA curve and post *a* wave pressure in the LV curve (cf. Braunwald et al. 1956 and 1961). The mean pressure in LA at rest showed good correspondence with the post *a* wave pressure in LV, while in a few cases dur

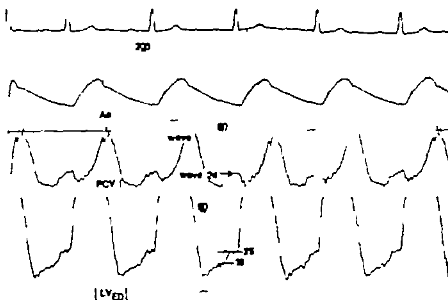


Fig 10 Central aortic, pulmonary capillary venous (PCV) and left entricular end-diastolic (LV_{ED}) pressure curves from patient with AI_{IV} combined with MI (No. 106). The peak wave pressure is indicated in the PCV curve, and the pre and post wave pressures in the LV pressure curve.

ing exercise large differences were obtained. The pressure decreases in LA during exercise in patients 84 and 106 are worthy of observation.

The *pneumonectomized patient* No 100, had raised pressures in PA and raised LV pressure: PA = 64, PA_D 28 PA_M = 41 and LV_{ED} = 26 mmHg. During exercise at ork load of 200 kpm min (corresponding to an O_2 uptake of 787 ml min) the pressures rose to the following alues. PA = 91, PA = 46, PA = 6_ and LV_{ED} = 36 mmHg. The diastolic pressure in the aorta rose from 71 mmHg at rest to 99 mmHg during exercise. The cardiac output increased from 6.1 l min at rest to 6.9 l min during exercise, hich corresponded to an "exercise factor" (increase in cardiac output in ml min per 100 ml min increase in O_2 uptake) of 189. The effective stroke volume decreased from 73 to 6_ ml.

Fig. 11 shows the *relationship* between the simultaneously measured *pulmonary capillary venous mean pressure* (PCV_M) and *LV end-diastolic pressure* determined at two diastolic levels, pre *a* wave and post *a* wa e. The mean difference between PCV_M and LV_{ED} "pre *a* wave $\pm$S.E.M., was 1.5 ± 0.5 mmHg, S.D 3.8 and between PCV_M and LV_{ED}, post *a* wa e -4.5 ± 0.6 mmHg, S.D 4.1 Both differences were significant ($P < 0.01$ and < 0.001 respectively) In the 7 patients in the right hand side of the figure with both PCV_M and LV_{ED} pre *a* wave higher than 12 mmHg, the early diastolic pressure in LV was 10.6 ± 1.0 (mean $\pm$S.E.M.) mmHg (group 1) In 13 patients in whom PCV_M was 12 mmHg or lower but LV_{ED} post *a* wave higher than 12 mmHg, the mean early diastolic pressure was 7.7 ± 0.7 mmHg (group 2) The difference in early diastolic pressure between these two groups was significant ($P < 0.05$) The mean relative heart volume in the patients in the former group was 806 ml/m² and in the latter group 615 ml/m² the difference between the two groups was significant ($P < 0.01$). A third group with a mean PCV pressure of lower than 12 mmHg and LV_{ED} post *a* wave also lower than 12 mmHg had a mean early diastolic pressure in LV of 4.0 ± 0.6 mmHg, which differed highly significantly from the early diastolic pressure in the two other groups ($P < 0.001$). The mean relative heart volume in this third group with a normal filling pressure was 585 ml/m² and differed highly significantly ($P < 0.001$) from group 1 with an elevated LV filling pressure (PCV LV_{ED} pre and post *a* wave") On the other hand there was no significant difference in relative heart volume between the second and third groups.

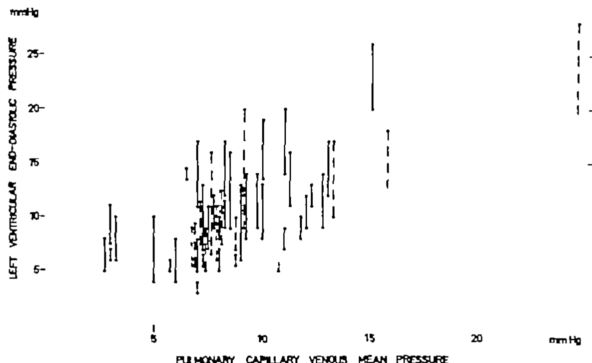


Fig. 11 Relationship between simultaneously measured pulmonary capillary venous mean pressure and left ventricular end-diastolic pressure determined at two diastolic levels, "pre wave and "post wave. These two levels are joined by vertical lines dotted AI_{II}, dashed AI_{III} and whole lines AI_{IV}

II. *Central Haemodynamic Findings*

The results of *flow measurements* at rest in men and women with different grades of AI are presented in Tables 23 and 26

Under *resting* conditions, the mean value for O uptake was essentially the same for the different AI grades but on the average somewhat lower for women than for men. In comparison with the calculated basal O uptake, the O_2 uptake during the catheterization was, on the average increased by 20%. The mean values for AVD_{O_2} lay within normal limits for the patients with AI and AI_{II} (and for the 3 women with AI_{III}) but for the other groups were slightly to moderately elevated. As seen in Table 23 both the effective flow and the effective stroke volume showed some tendency to a decrease with increasing grade of AI by a less than normal value especially for AI_{IV} + MI. The mean value for pulmonary vascular resistance lay essentially within normal limits and showed no appreciable difference between the different AI grades The values for pulmonary vascular resistance have been discussed earlier in chapter III, p. 33.

The results of flow measurements during *exercise* in men and women with different grades of AI are presented in Tables 24–26.

Figs. 12 and 13 illustrate the *relationship* between *O_2 uptake* and *arterio-venous O_2 difference* (AVD_{O_2}) at rest and during exercise in patients with different grades of AI. It can be seen in Fig. 13 that all patients with AI grades I and II had an AVD_{O_2} of less than 50 ml/l at rest, while the corresponding value for 2 patients with AI_{II} (Nos. 81 and 85) and a history of left ventricular failure was approximately 70 ml/l. One of these patients (No. 85) had the highest AVD_{O_2} (150 ml/l) during exercise at an O uptake of 725 ml.

The majority of the patients in group AI_{IV} had an AVD_{O_2} higher than 50 ml/l at rest. The patients with an AVD_{O_2} of more than 110 ml/l during exercise at an O uptake of less than 1 litre were all in an advanced stage of the disease with both a history of and haemodynamic signs of left ventricular failure.

Figs. 14 and 15 show that there is a relatively intimate *relationship* between the *oxygen uptake* and *cardiac output* (effective forward flow) in

Table 23 *Central haemodynamic findings at rest in male and female patients with isolated AI of varying degrees and in five patients with AI grade IV combined with MI*

HR = heart rate, $\dot{V}o_2$ = oxygen uptake, $AVDo_2$ = arterio-venous oxygen difference, Q = cardiac output, CI cardiac index, SV_f = effective forward stroke volume, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance

AI grade		HR (beats/min)	$\dot{V}o_2$ (ml/min)	$AVDo_2$ (ml/l)	Q (l/min)	CI (l/min per m²)	SV_f (ml)	PVR (mmHg per l/min)	SVR (mmHg per l/min)
I + II		4	4	4	4	4	4	4	3
♂	Mean	64	300	44.5	6.76	3.37	105	1.2	16 7
	Range	62-69	280-321	39.5–49 1	6.50–7 11	3.20–3.59	100–113	0.9–1 4	15.3–18.5
III		10	10	10	10	10	10	10	10
o	Mean	65	287	56 0	5.28	[illegible].80	83	1.8	21.2
	S.D	10	24	10 0	1.04	0.60	25	0.5	4 4
	S.E.M.	3	7	3.2	0.33	0 19	8	0.2	1 4
IV < 45		21	21	21	21	21	21	21	20
yrs	Mean	71	278	51 4	5 66	2.98	80	1.2	16.2
♂	S D	8	34	10.7	1.40	0 67	23	0 4	4 5
	S.E.M	1	7	2.3	0.31	0 15	5	0.1	1.0
IV ≥ 45		22	22	22	22	22	22	22	22
yrs	Mean	66	283	59.9	4.83	2.53	73	1.9	21.8
♂	S D	8	40	8.8	1.02	0 52	14	1 1	5.0
	S.E.M	2	8	1 9	0.22	0.11	3	0.2	1 1
IV + MI		5	5	5	5	5	5	5	5
♂ + ♀	Mean	74	275	66.7	4 05	2.18	55	1.8	23 8
	Range	68–87	228–310	53.5–78 5	3.17–4 73	1 80–2 54	43–66	0.9–2.7	18.9–28.4
I II		3	3	3	3	3	3	3	3
	Mean	85	236	47.3	5 00	2.96	63	1 6	22.9
	Range	68–118	217 248	42.9–51.3	4.52 5 67	2.79–3 12	38–81	1.2 1.9	16 6–28.3
III		3	3	3	3	3	3	3	3
	Mean	88	221	43.7	5 09	3.16	57	1.3	20.9
	Range	86–93	204–237	41.9–44 7	4 58–5 67	2 84–3 46	49–66	0.9–1.6	16 8–23.3
IV < 45		5	5	5	5	5	5	5	5
yrs	Mean	75	229	51 4	4 60	2.79	61	1.2	20.9
♀	Range	63–92	180–312	37 7–68 2	3.08–5.99	2 00–3.38	41 72	0.7 1.6	13 7 33 0
IV ≥ 45		3	3	3	3	3	3	3	2
yrs	Mean	68	209	50.1	4 29	2.43	62	2.5	27 4
	Range	61 77	179–245	43 0–56.1	3 19–5 69	1.88–3 08	48–74	1.2–4 1	25 6–29.2

different grades of AI at rest and during exercise. The regression lines drawn in the figures represent normal values for younger persons of ages 16–41 years and for older persons of ages 61–83 years (Jonsson 1967). The lines through the origin ($y = 0.0274 \times \dot{V}_{O_2}$ and $y = 0.0230 \times \dot{V}_{O_2}$) refer to persons at rest and the other lines ($y = 7.00 + 0.0057 \times \dot{V}_{O_2}$ and $y = 5.04 + 0.0056 \times \dot{V}_{O_2}$) to persons during exercise. It is evident from the figures that the values for effective forward flow observed in the present study are essentially lower than the normal values at a corresponding O uptake; this applies both to rest and exercise and especially to the patients with AI_{IV}. The deviation from the normal values is especially pronounced for some patients with the lowest values. These patients had both a history of and haemodynamic signs of left ventricular failure.

The *exercise factor*, i.e. the increase in cardiac output in ml/min per 100 ml/min increase in O_2 uptake can give some information on the functional capacity of the myocardium. In these last mentioned patients this was low (lower than 500). The mean exercise factors ($\pm$S.E.M.) for the different AI grades were: I + II 660 ± 35 ($n = 6$) III 663 ± 49 ($n = 13$) IV below 45 years 674 ± 30

Table 24 *Central haemodynamic findings during exercise in male patients with AI of varying degrees*

The values are given in relation to levels of exercise selected according to magnitude of O_2 uptake, ml min (see text p. 67).

$\dot{V}o_2$ = oxygen uptake, HR = heart rate, $AVDo_2$ = arterio-venous oxygen difference, Q = cardiac output, CI = cardiac index, SV_f — effective forward stroke volume, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance

AI grade	$\dot{V}o_2$ at work		HR (beats/min)	$\dot{V}o_2$ (ml/min)	$AVDo_2$ (ml/l)	Q (l/min)	CI (l/min per m²)	SV_f (ml)	PVR (mmHg per l/min)	SVR (mmHg per l/min)
I + II			2	2	2	2	2	2		1
♂		Mean	96	948	88 3	10 74	5 43	113	—	11.6
		Range	*90–101*	*915–981*	*85.6–91.0*	*10.68–10.79*	*5.24–5 62*	*107–119*		
	b		2	2	2	2	2	2	1	1
		Mean	113	1 390	98.2	13 72	6 65	122	0 9	10 1
		Range	111 114	1 201 1 499	94 8–101.5	12 67–14 77	6 06–7.24	111 133		
			2	2	2	2	2	2	2	2
		Mean	149	1 735	112.9	15 36	7.65	103	1.3	9 4
		Range	145–153	1 612 1 857	112.7 113 1	14.30–16 41	7 45–7.85	93–113	1.0–1.5	8.2–10.5
III			5	5	5	5	5	5	1	5
♂		Mean	103	739	90.1	8 44	4.53	87	1.8	15.8
		Range	75–117	550–899	71 9–106 5	6 11 10 93	3 49–6.43	61 146		11.0–21 1
	b		7	7	7	7	7	7	3	7
		Mean	106	1 213	100 2	12 25	6 50	118	1.6	11 5
		S.D	21.0	180	15.9	2 02	1 32	23 0	0.3	1.3
		S.E.M.	8 0	68	6 0	0 76	0.50	8 7	0 2	0 5
			4	4	4	4	4	4	4	4
		Mean	122	1 861	118 7	15 76	8 17	131	1 6	9.2
		Range	106–140	1 713–1 956	108 4–133 7	14 42–17.84	7 19–9 03	103–152	1.2–2 0	8 1 10 4
IV			16	16	16	16	16	16	3	15
<45 y		Mean	102	864	88.4	9 91	5 25	98	1 4	11.3
♂		S.D	9.9	116	13 9	1 67	0.85	16.3	0 2	2.2
		S E.M	2.5	29	3 5	0 42	0 21	4 1	0.1	0 6
	b		18	18	18	18	18	18	13	16
		Mean	119	1 251	102 6	12 35	6 53	105	1 5	9 7
		S.D	15.7	148	12.9	2 01	1 14	19.2	0 6	1 9
		S E.M	3.7	35	3 0	0.47	0 27	4.5	0.2	0 5
			8	8	8	8	8	8	7	6
		Mean	136	1 681	115.3	14.83	7.82	111	1 2	8.2
		S D	11.8	97	16 9	2 19	1 30	22.1	0 3	1 8
		S E.M.	4.2	34	6 0	0 77	0.46	7.8	0.1	0 7
IV			14	14	14	14	14	14	7	13
>45 y		Mean	95	844	111.0	7 71	4.16	83	3 4	17.0
♂		S D	14 4	122	16.3	1.38	0.75	21.2	2 4	4.7
		S.E.M.	3 8	33	4 4	0 37	0 20	5 7	0 9	1.3
	b		10	10	10	10	10	10	7	10
		Mean	109	1 168	109 6	10 66	5.46	99	1.8	13 0
		S D	12 7	151	9 7	0 99	0 60	15 7	0 6	1 7
		S E M.	4 0	48	3.1	0.31	0.19	5 0	0 2	0.5
			5	5	5	5	5	5	5	5
		Mean	139	1 742	126 9	13.73	6 81	99	1.2	10.5
		Range	128–149	1 578–2 049	119 2 147 5	12.79–15.48	5.68–7.28	89–111	0 8–1 6	7.6–13.1

(n = 25), IV above 45 years 593 ± 24 (n = 23) and AI_{IV} + MI 489 ± 86 (n = 5) In 10 patients with history of left ventricular failure the exercise factor was low—on the average 368 ± 39

Figs. 16 and 17 show the relationship between *effective stroke volume* and *heart rate* at rest and during exercise in patients with AI_{IV} below and above the age of 45 years. For mean values of heart rate and effective stroke volume at rest and during exercise (at work loads of W_1 and W_2 kpm/min) see Table 77

As is evident from the figures and the above

Table 25 *Central haemodynamic findings during exercise in female patients wi h isolated AI of varying degrees and five male and female patients with AI grade IV combined with MI*

The alues are given in relation to levels of exercise selected according to magnitude of O_2 uptake, ml/min (see text p. 67).

$\dot{V}o_2$ = oxygen uptake, HR = heart rate, $AVDo_2$ = arterio-venous oxygen difference, Q = cardiac output, CI = cardiac index, SV_f = effective forward stroke olume, PVR = pulmonary vascular resistance SVR = systemic vascular resistance

AI grade	$\dot{V}o_2$ at work		HR (beats/min)	$\dot{V}o_2$ (ml/min)	$AVDo_2$ (ml/l)	Q (l/mi)	CI (l/mi per m²)	SV_f (ml)	PVR (mmHg per l/min)	SVR (mmHg per l/min)
I+II	a		3	3	3	3	3	3	1	3
♀		Mean	126	728	84 0	8 94	5 27	74	2.3	14.5
		Range	110–151	635– 789	67.5 99 9	7.52 11.68	4 40–6.42	50–106		9.8–17 6
	b		2	2	2	2	2	2	2	2
		Mean	149	1 091	101.5	10.94	6.15	74	1 7	11 7
		Range	147 151	1051 1 131	89 9–113 0	9.31 12.57	5.38–6.91	62–86	1.5–1.8	9 7–13.7
III	a		4	4	4	4	4	4	3	4
♀		Mean	140	722	74 9	9 64	6 02	69	1.6	1 0
		Range	127 160	615– 812	63.1 81.8	9 14–10.45	5 63–6 61	65–74	1.3–2.1	10 3–13.5
	b									
		Mean	—	—	—	—	—	—	—	—
		Range								
IV			7	7	7	7	7	7	4	7
<45		Mean	123	760	97 1	8.20	4.99	68	1.6	16 0
y		S D	21.0	163	22.1	2.63	1 50	21 7	0.9	6 0
		S E.M.	8.0	62	8.4	0.99	0 57	8 2	0.5	2.3
	b		1	1	1	1	1	1	1	1
		Mean	128	1 050	102.2	10.27	6.34	80	1 4	11.3
		Range	–							
IV			3	3	3	3	3	3	1	2
>45 y		Mean	109	713	91.8	7.80	4 44	72	3.0	20 2
♀		Ra ge	99–120	623– 759	84.5–100.6	6.89– 8.95	4 05–4.84	57–83		18.0–22 4
	b		2	2	2	2	2	2	2	1
		Mean	126	1 069	100 4	10 66	5.99	85	1.3	13 9
		Ra ge	125–127	1056–1081	96.7 104 1	10.39–10.92	5 90–6 08	83–86	1.2 1.3	
IV+MI			4	4	4	4	4	4	2	4
♂		Mean	102	815	128.6	6 68	3.59	66	3.3	19 7
		Range	87 111	664–931	95.2 153 7	4.32 9 78	2.45–5.26	50–99	2.7–3.9	12.1 26 6
	b		4	4	4	4	4	4	4	4
		Mean	132	1 217	132.0	9.52	5.06	73	2.2	15 1
		Range	129–138	1 027–1 439	108 1 163 2	6.76–13.29	3 61 7 15	49–103	1 6–2 8	9 6–23 4

mean values both men and women of both age groups showed an increase in stroke volume dur ing the first work load compared with the resting value, and in the men this difference was signifi-cant ($P < 0.001$) and amounted to an average of 22 ml. At work load 2 the stroke volume ex hibited large variations, but on the average it re mained at approximately the same level in the patients below 45 years, in the older age group it increased further to some extent even during work load 2, but this change was not significant.

Figs. 18 19 and 20 show the *relationship* be tween the *mean pressure* in the *left atrium* and the *effective stroke volum* in different grades of AI at rest and during exercise. It can be seen in Fig. 18 that the resting pressure in all these pa-tients except one lay within normal limits and that the pressure in the majority of patients showed only a very slight change during exercise with an ensuing increase of the stroke volume. In 3 patients with AI_{II} and 1 patient with AI_{II} the pressure rose during exercise however to 15–20 mmHg. One patient (No 65) exhibited a completely deviating picture—the filling pressure was distinctly increased at rest and rose consider ably during exercise, while at the same time the effective stroke volume decreased slightly in contrast to the other patients, in whom it in-

Table 26. *Significances of differences in central haemodynamic factors between varying AI grades at rest and during exercise*

The values indicate $P <$ For abbreviations see Tables 24 and 25

AI degrees	HR	$\dot{V}_{O_2}$	AVD_{O_2}	$\dot{Q}$	CI	SV_r	PVR	SVR
I+II–III								
Rest			0.10					
Work								
Work b								
I II–IV<45 y								
Rest								
Work								
Work b								
I+II–IV>45 y								
Rest			0.001	0.02	0.005			
Work			0.02	0.02	0.01			
Work b								
I+II–IV+MI								
Rest			0.001	0.005	0.001	0.05		
Work			0.02	0.10	0.05			
Work b			0.05					
III–IV<45 y								
Rest							0.005	
Work		0.05						
Work b								
III–IV>45 y								
Rest								
Work a	0.02		0.001		0.02			
Work b								
III–IV+MI								
Rest			0.025	0.02	0.02	0.10		
Work a			0.005	0.10	0.05			
Work b								
IV<45 y IV>45 y								
Rest			0.01		0.02		0.005	0.001
Work					0.005			
Work b				0.025	0.02			
IV<45 y–IV+MI								
Rest			0.01	0.05	0.02	0.05		0.01
Work								
Work b	0.10					0.01		
IV>45 y IV MI								
Rest						0.02		
Work								
Work b	0.01		0.01					

creased. This patient had syphilitic AI with disabling angina pectoris.

It is seen in Fig. 19 that most patients with AI_{IV} below 45 years of age had a normal left ventricular filling pressure at rest—below 12 mmHg—and that during exercise it did not increase in the majority but showed a slight to moderate decrease with a simultaneous increase in the stroke olume. In some patients there was an increase of the filling pressure, however which in 3 patients was moderate but in 2 patients (Nos. 41 and 67) pronounced. Of these, the male patient had a history of left ventricular failure and both had considerable cardiac en largement with a total volume of 1 600 (955 ml/m²) and 1 800 ml (815 ml/m²).

Of the patients with AI_{IV} who were 45 years of age or older several had a left atrial mean pressure at rest that was higher than 12 mmHg, and in 11 patients it increased to more than 15 mmHg

Table 27 *Mean values of heart rate and effective stroke volume at rest and work (see Figs. 16 and 17)*

	Males				Females			
	< 45 years		> 45 years		< 45 years		> 45 years	
	HR	*SV*	*HR*	*SV*	*HR*	*SV*	*HR*	*SV*
Rest	76	82	66	74	76	61	68	62
		= 20		20		= 5		= 3
Work 1	102	103	101	87	119	69	109	72
Kpm/min	W	= 290	W	= 275	W	= 170	W	= 183
		= 20		= 19		n = 5		3
Work 2	130	105	122	100	131	70	126	85
Kpm/min	W	= 580	W	570	W_2	= 365	W_2	= 400
		= 20		= 10		= 3		= 2

during exercise in some cases with a simultaneous slight decrease in the stroke volume. Of these latter patients 3 had a history of left ventricular failure and all 11 had considerable enlargement of the heart with a mean total volume of 1 399 ± 28 ml (767 ± 27 ml/m²).

III. *Regurgitant Volume Determined by the Continuous Dye Infusion Method*

An attempt at determining the regurgitant volume by the continuous dye infusion method was made in 26 of the 81 patients in this series. In 6 patients the dilution curves from LV were unsatisfactory: in 1 case this was due to technical difficulties with the withdrawal syringe, in 2 cases to uncertainty in assessment of the plateau and in 3 cases to an unsatisfactory position of the transseptal catheter in the LV with a tendency in 2 cases for the catheter to slide back into the LA (one of these patients had concomitant MI).

1 *Reproducibility*

Duplicate determinations of the *plateau height* and *regurgitant fraction* were made in 17 and 16 cases, respectively. In 5 of these one of the curves was not acceptable and the calculations therefore comprised 12 and 11 duplicate determinations. The mean difference ($d \pm$ S.E.M.) in plateau height was 0.7 ± 1.8 mm and in regurgitant fraction 0.4 ± 1.4% thus neither of these differences was significant. In the investigation of the *effective forward flow* by the sudden injection method the *indicator concentration* was determined in blood that had been drawn through the polyethylene catheter (PE 160) from the *aortic arch* or *brachial artery* or through the transseptal teflon catheter from *LV*. Comparisons were made between the flow values obtained and gave the following results: the mean difference between sampling of blood in the aorta and brachial artery ($n = 6$) was 0.09 ± 0.12 l/min between LV and the brachial artery ($n = 9$) 0.18 ± 0.10 and between LV and the aorta ($n = 8$) 0.08 ± 0.10 l/min. Thus in no case was there a significant difference.

Comparisons between *duplicate* determinations of the *effective flow* in association with continuous dye infusion in 10 cases, with sampling of

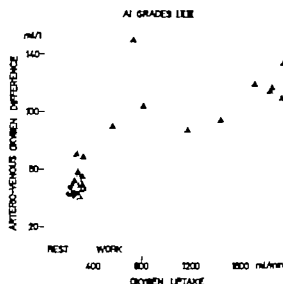


Fig. 17 Relationship between oxygen uptake and arterio-venous oxygen difference at rest and during exercise in male and female patients with AI grades I–III. Circles indicate females, triangles males. Asterisk = AI grade I; filled symbols = AI grade II; half-filled symbols = AI grade III.

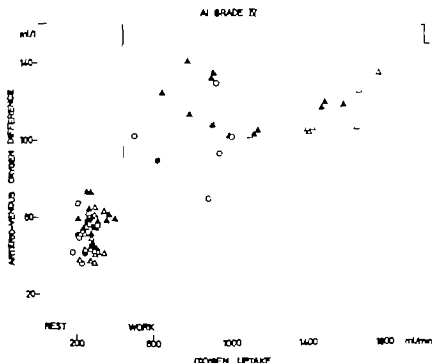


Fig. 13 Relationship between oxygen uptake and arterio-venous oxygen difference at rest and during exercise in male and female patients with isolated AI grade IV. Circles indicate females, triangles males. Open symbols indicate patients below 45 years of age and filled symbols patients 45 years of age or more.

blood from the *left ventricle* showed a mean difference of -0.015 ± 0.076 l/min

2. *Observations at rest*

Fig. 21 shows an example of a *continuous dye infusion curve* recorded *from LV* by the upstream sampling technique during infusion of indicator into the ascending aorta 1–2 cm above the plane of the aortic valve. The effective forward flow was determined a few minutes previously by sudden injection of dye into the right atrium and sampling of indicator from the brachial artery.

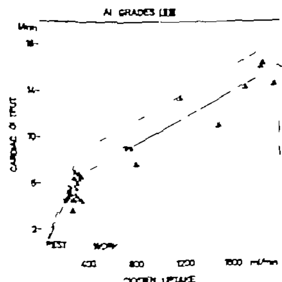


Fig. 14 Relationship between oxygen uptake and cardiac output at rest and during exercise in male and female patients with AI grades I–III. Circles indicate females, triangles males. Asterisk – AI grade I, filled symbols – AI grade II, half-filled symbols – AI grade III. Concerning the regression lines, which according to Jonsson (1967) represent normal material, see text; dashed lines represent the mean value for the age group 16–41 years and whole lines the age group 61–83 years in the normal material.

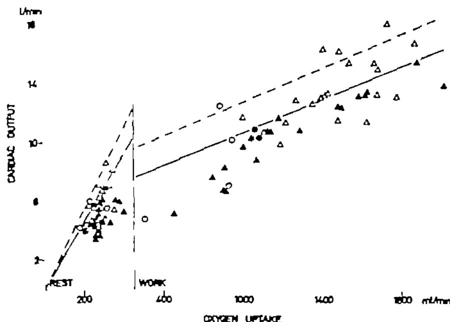


Fig 15 Relationship between oxygen uptake and cardiac output at rest and during exercise in male and female patients with isolated AI grade IV Circles indicate females, triangles males. Open symbols indicate patients below 45 years of age and filled symbols patients 45 years of age or more.

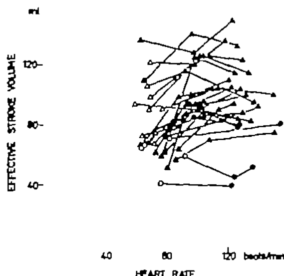


Fig 16. Effective stroke olume in relation to heart rate at rest and during exercise in male and female patients with isolated AI grade IV below 45 years of age Circles indicate females, triangles males. Open symbols = values at rest; filled symbols = values during exercise.

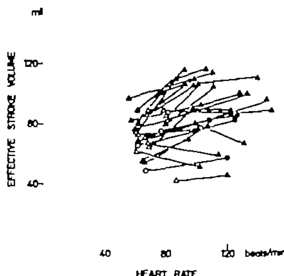


Fig 17 Effective stroke volume in relation to heart rate at rest and during exercise in male and female patients with isolated AI grade IV 45 years old or more. Circles indicate females, triangles males. Open symbols = values at rest, filled symbols = values during exercise.

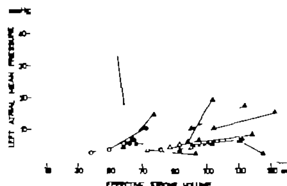


Fig. 18. Relationship between effective stroke volume and left atrial mean pressure at rest and during exercise in male and female patients with AI grades I–III. Circles indicate females, triangles males. Open symbols – values at rest; filled symbols – values during exercise, dotted line – AI grade I, dashed line – AI grade II, whole line – AI grade III.

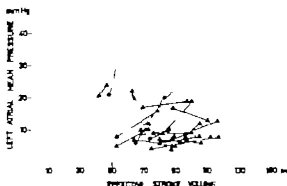


Fig. 20. Relationship between effective stroke volume and left atrial mean pressure at rest and during exercise in male and female patients with isolated AI grade IV 45 years old or more. Circles indicate females, triangles males. Open symbols – values at rest, filled symbols – values during exercise.

For assessment of the LV dilution curve both *shape and time criteria* were used. In the few isolated cases where owing to recirculation it was difficult to distinguish a definite plateau merely by inspection of the curve correction for the recirculation was made and the asymptotic level that the plateau would have reached was determined. This is possible as the upper part of the curve has a semilogarithmic function (Guyton 1963) Concerning the time criterion, a comparison was made between the time points for the recirculation that were obtained from the continuous dye infusion curve and from a sudden injection curve that had been recorded immediately before or after the infusion curve. In doing this an estimation was made of the time interval from the beginning of the appearance

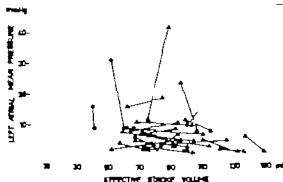


Fig. 19. Relationship between effective stroke volume and left atrial mean pressure at rest and during exercise in male and female patients with isolated AI grade IV below 45 years of age. Circles indicate females, triangles males. Open symbols – values at rest; filled symbols – values during exercise

$\dot{Q}_f$ 5.760 l/min A_f 95.9 mm

$$\dot{Q}_R \quad \frac{5.760}{\frac{95.9}{67} - 1} \quad 13.4\ \text{l/min} \quad 70\%$$

SV_t 304 ml

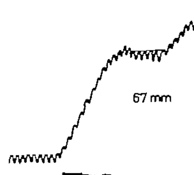


Fig. 21. Continuous dye infusion LV curve of male patient (No. 69) with AI grade IV. The values given in the figure are calculated from the equations given under Methods. $\dot{Q}$ – effective forward flow (measured by the sudden injection method)· A – the height of the calculated plateau from the base line of the arterial dilution curve; Q – regurgitant flow. SV – total stroke volume.

which was due to an increase of 83.5 (range 65–114)% in the effective flow. The mean decrease in regurgitant volume in these patients was 61.8 (range 44–85)% and in stroke volume 1.5 (range −14 to +12)%; the latter difference was not significant. In the 2 patients (Nos. 93 and 113) with a decrease in total flow of 38 and 11% during exercise, there was a relatively small increase in the effective forward flow of 40 and 44% respectively; further, in patient 93 there was a simultaneous large decrease in the regurgitant volume, of 76% at an increase in heart rate of 37 beats/min. In patient 113 the decrease in regurgitation was smaller at an increase in heart rate of only 17 beats/min. For all 6 patients the mean regurgitant fraction was 43.8 ± 9.3 (S.E.M.)% at rest and 20.0 ± 8.8% during exercise. The difference was significant ($P < 0.01$).

The *relationship* between the increase in *heart rate* and the decrease in *regurgitant volume* during exercise is illustrated in Fig. 25. The coefficient of correlation (r) was −0.953 (the lower *limit for confidence limit 95% of r was 0.38*) and the residual standard deviation from the best straight regression line 7%.

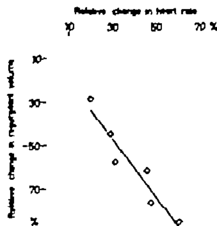


Fig. 25. Relative change in regurgitant volume (l/min) determined by the continuous dye infusion method in relation to relative change in heart rate during exercise test. Correlation coefficient = −0.953.

IV. Complications

1. Arterial complication

In 4 of the patients heavy bleeding occurred after percutaneous arterial puncture (brachial artery in 1 patient and femoral artery in 3 patients) necessitating evacuation of the haematoma and suturing of the artery. In an analysis of complications during heart catheterizations performed in 16 leading cardiovascular centres in the United States (Braunwald and Swan 1968) this increased risk of false aneurysms as a complication of arterial catheterization in patients with AI with a wide pulse pressure was pointed out.

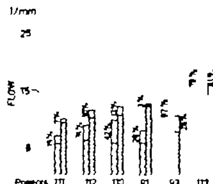


Fig. 24. Effective forward, regurgitant and total flows measured by the continuous dye infusion method at rest and during exercise test, in patients with pure AI of varying degrees and 1 patient with AI combined with slight MI. The flows are given in l/min and the regurgitant fraction also in per cent of the total flow. Widely cross-hatched bars = effective forward flow at rest, narrowly cross-hatched bars = effective forward flow during exercise test; unfilled bars = regurgitant flow.

2. Complications of transseptal left heart catheterization

(a) *Atrial fibrillation* was elicited in one patient during manipulation of the catheter in the right atrium prior to septal puncture. During the subsequent work test there was a change-over to sinus rhythm.

(b) *Vasovagal attack*. One patient developed bradycardia and hypotension without pain during an attempt at puncture of the atrial septum and further attempts at transseptal catheterization were therefore abandoned. The patient recovered after a few minutes and the remaining part of the investigation could be completed as planned.

3. Arrhythmia

During the work test in association with heart catheterization one patient had transient atrial fibrillation, which spontaneously changed to sinus rhythm after completion of the work test.

The complications that occurred in connection

with the angiocardiographies are reported in the chapter on angiocardiographic examinations.

DISCUSSION

In AI the volume overload of the left ventricle is the basal haemodynamic abnormality. As is evident from the present series, even in cases with pronounced regurgitation fairly normal intracardiac pressures and flows can be found in an early well compensated stage of the valvular disease. This has also been pointed out by Krayenbühl (1969) and Lewis et al. (1970) among others.

I. *Intracardiac Pressures and Central Haemodynamic Findings*

With regard to the *pressures at rest* it is of especial interest to note that in this series of patients the diastolic pressure in the aorta lay on the average, as high as at about 60 mmHg in AI grade IV with maximal values up to about 85 mmHg, even in cases without decompensation. As mentioned previously in chapter IV the diastolic arterial pressure is often used as a rough clinical measure of the degree of severity of the aortic incompetence. For this purpose, however the lower indirectly measured peripheral brachial arterial pressure, which is generally reported to lie at 50 mmHg or lower in severe AI (cf. Friedberg 1966) is mostly used. During exercise in the present study the diastolic aortic pressure increased in patients with AI_{IV} by an a erage of about 35% of the value at rest, which is more than is usually found in normal subjects (Holmgren 1956). The increase in the diastolic arterial pressure found in this series of patients agrees well with that obtained by Lee et al. (1971) in preoperative xamination of 10 patients with AI. After operative correction of the al ular lesion they found a considerably smaller increase, of only 13%.

As has been pointed out by Jones et al. (1964) Miller et al. (1965) and Gault et al. (1970) the LV dilatation in AI constitutes a compensatory response to the increased load on the left entricle brought about by the regurgitation, and at this compensatory stage need not result in any increase in the LV end-diastolic pressure. Relatively large changes in EDV can be accompanied by relatively small changes in LV_{ED} pressure. According to these authors, haemodynamic signs of reduced ventricular performance are a consequence of depressed myocardial function and not primarily a result of the increased haemodynamic burden due to overloading. Thus in these patients heart failure would be the result of an increased mechanical load together with myocardial failure (cf. Dodge and Baxley 1968. Braunwald and Ross 1963).

The *LV filling pressure* measured just before the ventricular contraction (Braunwald et al. 1956) has been widely used as an index of LV function but as pointed out by Braunwald and Ross (1963) and Falicov and Resnekov (1970) LV_{ED} pressure can be influenced by other factors than the muscle function *per se* e.g. LV compliance. In LV failure the diastolic LV pressure is increased throughout diastole, thus even in early diastole, while in reduced LV compliance only the end-diastolic pressure is elevated. One cannot therefore place too great weight on this measure alone of the LV functional capacity. The pump function of the left ventricle can be assessed with more reliability by studying at the same time the change in the LV end-diastolic pressure and stroke volume that appears during exercise (Ross et al. 1966, Ross 1969. Rackley et al. 1970). This was pointed out in 1954 by Sarnoff and Berglund, who by the construction of ventricular function curves in dog experiments found that the ventricular filling pressure was an important regulator of the stroke work.

In investigations of healthy subjects of different ages in the supine position, Holmgren et al. (1960) Granath et al. (1964) and Ekelund and Holmgren (1967) among others, found an increase in stroke volume of 8–13% at a change over from resting conditions to moderate exercise. On a further increase of the work load the stroke olume emained unchanged or decreased towards the value at rest.

The pattern of *response* of the *left ventricle* to *muscular xercise* in patients with and without LV dysfunction has been studied by Ross et al. (1966) and others. The LV performance has since been discussed by Ross (1969). These authors differentiated 3 types of response to supine muscular exercise: (1) an increase in stroke volume while LV_{ED} pressure remained unchanged or decreased, in patients with normal LV function (2) an increase in both stroke volume and LV_{ED} pressure as a sign of mild LV dysfunction (3) an increase

in LV_{ED} pressure while the stroke volume remained unchanged or decreased, as an expression of depressed LV function.

All these three types of response were observed in the present series of patients with AI. In about one third of the patients the LV filling pressure decreased during exercise while at the same time the effective stroke volume increased. The effective stroke volume increased during exercise by an average of about 25–35% of the resting value, which is considerably more than was found by Holmgren et al. (1960) and Ekelund and Holmgren (1967) in normal subjects. Lee et al. (1971), who investigated patients with severe AI, found a still greater increase (48%) in the stroke volume during exercise. This marked improvement in the circulatory dynamics during exercise in patients with AI without myocardial failure is assumed to be due to a shortened length of diastole during muscular work with a simultaneous decrease in the regurgitant volume. This might also partly explain the decrease in LA pressure observed during exercise in 2 of the present patients with AI and MI combined. With the decrease in the amount of blood regurgitating through the aortic ostium and the decrease in the end-diastolic volume during exercise, it is theoretically conceivable that there would be a decrease in the regurgitation to LA, which may be secondary to the LV dilatation due to AI.

Sarnoff and Berglund (1954) mentioned the difficulty in determining the end-diastolic pressure at a high heart rate. For this reason they preferred to use the mean pressure in LA as a measure of the LV filling pressure—they had found a satisfactory correlation between the mean pressure in LA and the end-diastolic pressure in LV in the low and medium ranges. Braunwald et al. (1961) in agreement with these results, found on examination of persons without heart disease that the LV_{ED} pressure differed very little from the mean LA pressure or from the atrial pressure at the onset of LV contraction (the z point). Forsberg (1971) arrived at the same result on investigation of patients with varying cardiac diseases. Sapru et al. (1968) also found a close correlation between the z point pulmonary arterial wedge pressure and the LV_{ED} pressure both at rest and during supine exercise. In 95% of normal subjects the difference was not greater than ±1 mmHg at rest and ±2 mmHg during exercise.

On comparison between the diastolic pressure in LA and LV—measured immediately before the "a wave" and at the z point—in patients with AI+MI in the present series, good agreement was obtained between LA and LV pressures measured at these two levels. On the other hand there was a relatively large difference in some cases between the mean pressure in PCV and the LV_{ED} pressure at the z point level ("post a wave"), measured simultaneously. Relatively good agreement was obtained, however, between the mean PCV pressure and the diastolic "pre a wave" pressure in LV. Patients with greatly increased end-diastolic LV pressure with elevation of both the "pre and post a wave" levels and a large discrepancy between these levels differed significantly from patients with a normal "pre a wave" level both as regards the early diastolic pressure and heart size. Thus it appears that a study of the end-diastolic pressure in LV in these patients with severe AI can give more information on the functional capacity of the left ventricle than the mean pressure in PCV or LA alone. Lewis et al. (1970) also found in patients with severe AI that the mean LA pressure was distinctly lower than the end-diastolic pressure in LV, which they assumed to be due to a vigorous atrial systolic contraction.

II. *Flow Determinations with the Dye Dilution Technique in AI*

1. *General aspects*

(*a*) *Effective forward flow.* In a study comprising 298 catheterizations of patients with AI of varying degrees of severity Samet et al. (1966) found no significant difference in the cardiac output between sampling of blood from the pulmonary artery and a systemic artery after injection of indicator dye into the right atrium. The systemic arterial indicator dilution curve thus can be considered to give a valid measure of cardiac output even in severe aortic regurgitation. In the more advanced cases and in patients with additional heart failure the semilogarithmic extrapolation of the downslope of the curve can offer difficulties. Even in this type of curve, however, good agreement was found in the present series between the dilution curve area calculated planimetrically by the two ways mentioned under Methods, with and without semilogarithmic plotting.

(*b*) *Left ventricular and aortic mixing* In the upstream sampling technique with injection of indicator into the aortic root and sampling of indicator in LV the mixing conditions in the aorta and LV are of decisive importance. This has been greatly discussed and different opinions have been expressed. Irisawa et al. (1960) and Swan et al. (1960 and 1965) concluded from dog studies that the ventricular mixing was inadequate. The former authors measured the conductivity in two places in LV after injection of saline into this ventricle They found a delayed spread of indicator in the apical portion of LV but after 3–4 beats a fairly uniform concentration throughout the ventricular volume was achieved in over 75% of the records. Swan and Beck (1960) found after injection of dye into the LV and sampling at two sites in the ascending aorta just above the aortic val e that the first portion of blood of each systole was less dyed than the portion at the end of systole. In these studies, as well as in later investigations with injection of cold saline into the aorta and recording with two thermistors in the aorta, they found that concentration differences occurred within the aortic root which they considered to function as a mixing chamber

Freis and Heath (1964) on the other hand, using the thermodilution method in dog experiments, showed that the indicator which was in fused in different parts of the aorta including the aortic root, spread evenly over the greater part of the aortic diameter within the ascending area. They assumed that the blood that was ejected into the aorta during systole produced a disturbed flow in the central part of the ascending aorta, in contrast to the streamlined flow in the descending portion. The mixing took place primarily during systole but might have been caused partly by the backflow during early diastole in this part of the aorta.

In determining the left ventricular end-systolic volume by the thermodilution technique, Rapaport et al. (1961) obtained good reproducibility which they interpreted as indicating relatively complete mixing of temperature in the ventricle

With *incompetent valves*, it is conceivable that owing to increased turbulence the regurgitating blood flow may giv improved mixing in the chamber receiving the regurgitant jet (cf Conn et al. 1957) In model studies Levinson et al. (1963) were able to reproduce the curve appearance seen in MI by enhancement of mixing in the left atrium.

In a study of the *mixing* conditions in *LV* Armelin et al. (1963) injected dye into the aorta of dogs with *AI* and found almost identical areas beneath two simultaneously recorded dilution curves from two different sampling sites in LV In one case they made a comparative study of the regurgitant fraction determined by sampling in the inflow and outflow tracts and in the apical region of LV without finding any systematic dif ference between these different sampling sites Carleton et al (1965) concluded from experiments with sodium ascorbate as indicator that in complete mixing in LV could result in falsely high alues for EDV compared with the alues obtained on angiographic determination. In one pa tient with AI they did not find this discrepancy however which they considered to be due to bet ter mixing conditions with this valvular lesion

On determination of the regurgitant fraction in *combined AI and MI* with sudden injection of dye into the ascending aorta and injection into LV during 1 1/2 cardiac cycles and sampling of indicator from LV and the femoral artery and from LA and the femoral artery respectively Bloomfield et al. (1966) found a high correlation between the product of the regurgitant fraction for the leakage through the mitral alve alone and the aortic al alone and the combined fraction obtained across both valves ($r = +0.99$). They considered this finding to indicate that the mixing in the left ventricle was good.

In the present series of patients *good agreement* was obtained between the values for the *effective flow* obtained on *sampling of indicator* from the *brachial artery* the *aortic arch* and *LV* Further the good correspondence observed between *duplicate* determinations with *sampling* of blood from *LV* would hardly be expected if the mixing in LV had been poor In all of these patients the transseptal catheter was placed with its tip in the mid-portion of LV which is probably of still greater importance in the upstream sampling method—in a few cases studied with continuous dye infusion the curves obtained were not acceptable, as the tip of the catheter happened to have slipped towards the mitral valvular plane.

On *simultaneous* determination of the regurgitant fraction in AI in dogs by an *electromagnetic flow meter* and *continuous dye infusion*

into the ascending aorta, Frank et al. (1966 *b*) obtained good correlation ($r = +0.92$) between these two completely different methods of measurement. This indicates that with the upstream sampling method representative samples are obtained from LV which in turn points to satisfactory mixing in LV in patients with aortic incompetence.

The same authors (1966 *a*) in a study of the *regurgitant volume* in patients with AI compared results obtained with the *sudden injection technique* (the injection randomly timed with respect to the cardiac cycle) and the *continuous dye infusion method*. They convincingly demonstrated the superiority of the latter method in which the scatter is small, the reproducibility good and the error of estimate at a confidence limit of 95% 4 times smaller than with the sudden injection technique (for the regurgitant fraction 9% and 36% respectively). An important source of error in this latter method, with decisive influence on the evaluation of the regurgitant volume is the varying time point during the cardiac cycle at which the injection is given; this has been shown in dog experiments by Armelin et al. (1963) and by other authors. A further source of error as pointed out by Frank et al. (1966 *a*) is the variations in flow from one beat to another.

As mentioned by these authors, among others, the *regurgitant fraction* (the ratio between the regurgitant and total flow) constitutes the best measure of regurgitant volume. They found good agreement between the angiographically established grade of incompetence and the regurgitant fraction, while no such relationship was observed with respect to the absolute values of regurgitant volume and total flow. Mild regurgitation—grade I angiographically—corresponded in their studies to a regurgitant fraction of less than 25%, and in severe regurgitation the fraction was over 75%. In the present series, patients with AI grade IV according to thoracic aortography exhibited greatly varying values for the regurgitant fraction—from a minimum of 33% to 76%—and it seemed justifiable therefore to divide the large AI_{IV} group into two sub-groups (see chapter VII p. 98).

The mixing conditions in the aortic root in patients with AI have undergone a critical study by Frank et al. (1966 *a*) who compared the values for effective flow obtained on continuous dye infusion into the aortic root and sampling of indicator in the brachial artery with those obtained on sudden injection of dye into the pulmonary artery and sampling of blood from the aortic root. The mean difference between these two determinations was 0.08 l/min and not significant, which may be considered to indicate satisfactory mixing in this part of the aorta. The authors found equally good reproducibility of the regurgitant fraction regardless of whether the upstream and downstream curves were measured simultaneously or non-simultaneously in rapid succession.

(c) *The position of the tip of the catheter* in the ascending aorta is another important factor in the injection of indicator above the aortic valvular plane as shown by Armelin et al. (1963) and will be discussed in more detail in chapter VII p. 120.

2. *Exercise and regurgitant volume*

As mentioned previously, even patients with a severe degree of AI and considerable cardiac enlargement usually have a surprisingly good physical work capacity as long as the disease is in a compensatory stage. It has long been known that an increase in the heart rate decreases the duration of diastole more than that of systole (cf. Warner and Toronto 1961 and Rothlin et al. 1968). As early as in 1832 Corrigan expressed the view that a rapid heart rate reduced the severity of aortic regurgitation. The favourable effect of *tachycardia* in patients with AI has been studied and confirmed by several investigators, who have increased the heart rate by electrical stimulation of the right atrium.

Warner and Toronto (1961) studied the effect of an increase in the heart rate by 36–45 beats/min on the distance of aortic backflow determined by a dye dilution method in 3 patients with AI. At the higher heart rate (105 or 120/min) they found a decrease in backflow distance per stroke to less than half the distance at the slower rate.

Opinions differ as to the reason for the improvement, especially as deviating results have been obtained as regards the flow changes associated with an increase in heart rate. Thus Rutishauser et al. (1967) using the thermodilution technique, found a marked decrease in total flow and regurgitant volume and a simultaneous

increase in effective flow on increasing the heart rate. The maximal effective cardiac output was reached at a heart rate of 100–120/min, but on further increase of the heart rate the cardiac output again began to decrease slightly. These findings have since been verified by Rothlin et al. (1968) on determining the regurgitant volume by calculating the distance of aortic regurgitation by means of the dye dilution technique and an ear piece densitometer. These authors found a reduction in the distance of aortic regurgitation by an average of 39% of the initial value at a mean heart rate increase up to 159%. A further increase of the heart rate was not accompanied by any appreciable decrease of the regurgitant volume.

In conflict with their results, Brawley and Morrow (1967) who made flow determinations with an electromagnetic flow meter in connection with operation on the valvular lesion, found no reduction in the regurgitant fraction in association with an increase in the heart rate. According to these authors, the absence of the expected decrease in the regurgitant fraction could be explained by the fact that in their 6 cases a decrease occurred in the rate of systolic ejection, while the rate of regurgitant flow remained relatively constant in 4 of these 6 cases. In agreement with these findings Wiggers (1931) from an analysis of curves from the aorta and left ventricle recorded in dogs, had predicted that an increase in the heart rate would have only a very slight effect on the degree of severity of the regurgitation since only the last part of diastole is eliminated on an increase of the heart rate and during that time the regurgitant blood volume is at its smallest. The same result as that of Brawley and Morrow was arrived at by Judge et al. (1971) who calculated the regurgitant volume by subtracting the effective flow determined by the Fick method from the total flow calculated angiographically. Even though this combined method is theoretically free from objection, in practice several factors can contribute to limiting the precision in the determination of the regurgitant volume (see chapter on angiocardiographic examination, p. 119) and it is therefore possible that difficulties will be encountered in detecting minor changes in flow. The results of Brawley and Morrow are rather difficult to evaluate since the investigations were performed under general anaesthesia with an open chest and at a low effective cardiac output.

Rutishauser et al. (1967) and Judge et al. (1971) reported a significant decrease in the end-diastolic volume and end-diastolic pressure in association with an increase in heart rate. The latter authors also found a marked reduction in the end-diastolic circumferential stress and end-diastolic load of the left ventricle.

There is a considerable difference between the haemodynamic changes that occur with pacemaker induced *increase in the heart rate* and those that result *from muscular work*. In the latter case positively inotropic influences act to maintain or increase the stroke volume. Further during muscular work the peripheral vascular resistance decreases, which facilitates the peripheral run off of blood and contributes to reducing the regurgitant volume. In the present series 6 patients showed a significant decrease of the regurgitant volume ($P < 0.05$) and regurgitant fraction ($P < 0.01$) and a significant increase of the heart rate and the effective forward flow ($P < 0.01$). In the 4 patients with an increased total stroke volume this change was also significant ($P < 0.01$). The number of observations was small but the findings agree essentially with the results published by Levinson et al. in December 1970 from a comparative study of the mode of reaction to work loads in 5 patients with MI and 5 with AI in which they used the continuous dye infusion technique for determining the regurgitant volume.

Of the 2 patients in the present series in whom the total flow decreased during exercise, patient 93 had considerable cardiac enlargement with a total volume of 1 510 ml and atrial fibrillation with normal ventricular frequency as well as a history of LV failure but on catheterization a normal end-diastolic pressure in LV was found and, as mentioned previously, clinical and haemodynamic signs of MI although not verified angiocardiographically. According to Bloomfield et al. (1966) and Frank et al. (1966 *b*) concomitant MI —especially if mild—would not affect the precision in an evaluation of the aortic regurgitation.

The correlation between the percentual increase in heart rate and the decrease in regurgitant volume in the 6 patients in the present series may be regarded as relatively certain, despite the small number of observations, since the residual

standard deviation (S D.$_{p}$) from the best straight regression line was only 7% Contributory to the percentual decrease in regurgitation in these patients was not only the reduced duration of diastole resulting from the heart rate increase but also the increase in the systolic ejection rate during muscular work, which has been pointed out by Brawley and Morrow (1967) among others.

CONCLUSIONS

In an early well compensated stage of the valvular disease fairly normal intracardiac pressures and flows were found As in normal subjects there was a linear correlation between O_2 uptake and cardiac output, but in patients with pronounced AI the effective flow was generally lower than the corresponding normal values. This finding was especially pronounced in patients with a history of LV failure and these patients showed a low exercise factor" namely 368 while the corresponding mean value in patients with AI grades I and II with no signs of LV dysfunction was 660. This value is in good agreement with the lower normal limit of 600 given by Ross et al. (1966)

During muscular exercise in the supine position the regurgitant blood volume decreased and an intimate relationship was found between this reduction in the regurgitant fraction and the increase in heart rate. This might partly explain the improved circulatory dynamics, with a decreased LV filling pressure and an increased effective stroke volume observed even in patients with severe AI but with a good functional capacity In several patients with severe AI the effective stroke volume decreased while at the same time the LV filling pressure which was already elevated at rest increased further which was interpreted as a sign of depressed myocardial function. Further during exercise there was mostly a higher increase in the diastolic arterial pressure than in normal subjects.

On comparison between simultaneously recorded PCV and LV_{ED} pressures, in severe AI a high diastolic LV pressure was found both at the beginning and end of diastole. The pressure increase at the end of diastole measured at the point of onset of LV contraction was pronounced, and lay at a considerably higher level than the mean PCV pressure which corresponded better to the pre *a* wave pressure level

VI EFFECT OF AMYL NITRITE INHALATION

Phonocardiographic observations and central haemodynamic findings

As an aid to the bedside diagnosis of cardiac murmurs, different vasoactive drugs have come into use. Of these, amyl nitrite, which is a peripheral vasodilator is used most commonly This drug is easily administered by inhalation, its effect is rapid and of short duration (1–2 min) and the side-effects are few Amyl nitrite was first tested in 1867 by Brunton as a pain-relieving agent in angina pectoris. Its importance for the differential diagnosis of murmurs was pointed out by Kahler 1933 and has since been studied by several authors (Barlow and Shillingford 1958 Bousvaros and Lesof 1962 Endrys and Bártová 1962, Richter et al. 1967 O'Rourke 1970) The haemodynamic effects of amyl nitrite are well known and are due to a reduction of the total peripheral vascular resistance with an accompanying marked decrease of the systemic arterial pressure and secondary increase of the heart rate and an increase of the cardiac output (Beck et al 1961 Perloff et al. 1963, de Leon and Perloff 1966).

In patients with *AI* this inhalation test has gained wide practical use for differentiation of the apical diastolic murmurs in AI, named the Austin Flint murmur from the murmur of organic MS (Currens et al. 1953 Segal et al. 1958, Kiger 1963 Nasser et al. 1966) Even in those cases where there is difficulty in deciding whether the basal diastolic murmur arises from pulmonary insufficiency or aortic insufficiency the amyl nitrite test can be of diagnostic value (Soh 1960, Ranco et al. 1961).

The investigations described below were carried out in patients with AI of grades III and IV partly to obtain an idea of the validity of the amyl nitrite test as a diagnostic aid in investigation of patients with confirmed AI, and partly to study the central haemodynamic effect of a decreased peripheral resistance

METHODS

Phonocardiogram (PCG) (see under Methods, chapter IV p 35) This was recorded in 38 patients before and during amyl nitrite inhalation. The microphone was as a rule placed in the 3rd or 4th intercostal space in a few isolated cases in the 2nd intercostal space at the left sternal border and in some cases in the 2nd intercostal space at the right sternal border In 5 patients with a fairly low-frequency apical presystolic murmur a recording was also made over the apex During a control period ECG and PCG were recorded simultaneously and the heart rate was counted from the ECG After the control period amyl nitrite was inhaled for about 60 sec from a small piece of gauze which had been soaked with the drug from two ampoules (0 1 g each) the gauze being held under the nostrils. ECG and PCG were recorded continuously during the inhalation. The amplitude of the diastolic murmur was measured before the inhalation and at the peak effect of the amyl nitrite, when the heart rate was also counted.

Pressure and flow measurements

Towards the end of the heart catheterization, simultaneous recordings of ECG and the pressures in the aortic arch, PCV and LV were made in 23 patients with AI grades III and IV (in a few cases the LV pressure was not recorded) both during a control period and continuously during inhalation of amyl nitrite (0.2 g) The pressure changes at the peak effect of the amyl nitrite (30–40 sec after the start of inhalation) were noted. In 10 patients the cardiac output was determined by the dye dilution technique (see under Methods, chapter V p. 63) both during a control period and during inhalation at the height of the amyl nitrite effect, which in these cases also occurred 30–40 sec after the patient started

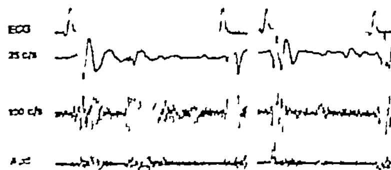


Fig. 26. Phonocardiogram (PCG) and electrocardiogram (sinus rhythm) of 62-year-old man with AI grade IV (No. ?). PCG recording from the 2nd right intercostal space at the sternal border before amyl nitrite inhalation and during the inhalation of the height of its effect. The amplification was 1/5. Filters with nominal frequencies of 25 and 100 c/ and one auditory filter were used. The paper speed was 100 mm/sec. The heart rate before inhalation was 67 beats per minute and at the peak effect of the amyl nitrite 30 sec after the start of inhalation 100 beats per minute. At this time point the high-frequency diastolic murmur has almost disappeared.

to exhale. As the above-mentioned pressures and flow could not be determined at the same time the amyl nitrite test was repeated in 6 cases after 15 min, when the effect of the first inhalation had disappeared, for complementation of pressure or flow measurements.

RESULTS

I. Phonocardiographic Observations

1. High frequency diastolic murmur

In the 38 patients in whom the effect of an amyl nitrite inhalation on the *basal diastolic AI murmur* was studied, the following changes in the amplitude of the PCG recording of the murmur were noted at the height of the amyl nitrite effect 30–60 sec after the start of the inhalation. (1) In 5 cases there was no change (2) in 17 cases there was a decrease to about half of the initial amplitude, (3) in 8 cases there was a decrease by more than half and (4) in a further 8 cases the murmur almost completely disappeared (a decrease to more than 80%). Fig. 26 shows the PCG from a patient with AI grade IV in whom the murmur practically disappeared during amyl nitrite inhalation at this time point the heart rate increase was 33 beats per min. For the above 4 different groups the mean heart rate increases were: 29 (40%) 28 (36%) 31 (50%) and 26 (37%) beats per minute. In group 1 with no change in amplitude during the inhalation 1 patient had an increase in heart rate of only 8 beats per min.

2. Low frequency diastolic murmur

On auscultation as well as in the PCG recording a *low frequency diastolic murmur* with *presystolic crescendo* similar to that described originally by Austin Flint (1862) was noted over the *apex* in 5 patients. In all of these patients the presystolic murmur decreased clearly in amplitude and in a few cases practically disappeared, during the inhalation, as is illustrated in Fig. 27 which shows the recording of the presystolic murmur over the apex in one of them (No. 65) before and during amyl nitrite inhalation (30 sec after the start of the inhalation). The left ventricular end-diastolic pressure ("post *a* wave") was elevated in all these 5 patients, with a mean value of 23 (range 16–30) mmHg, while the pulmonary capillary venous mean pressure was somewhat lower with a mean value of 18 (range 9–27) mmHg. During amyl nitrite inhalation the mean LV_{ED} pressure in 4 of these patients was 5 (range 1–12) mmHg and the mean value for PCV mean pressure 7 (range 4–11) mmHg. The end-diastolic volume of the left ventricle in the 5 patients was greatly increased and amounted to 485 ± 38 ml (mean $\pm$ S.E.M.)

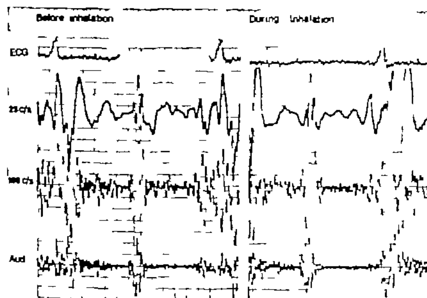


Fig 27 Phonocardiogram (PCG) and electrocardiogram (sinus rhythm) of 60-year-old man with AI grade III (No. 65). PCG recording over the apex with the patient lying on his left side before amyl nitrite inhalation and during the inhalation at the height of its effect. The amplification was 1/10. Filters with nominal frequencies of 25 and 100 and one auditory filter were used. The paper speed as 100 mm/sec. The heart rate before inhalation as 80 beats per minute and at the peak effect of the amyl nitrite 30 sec after the start of the inhalation 100 beats per minute. At this time point the presystolic murmur has almost disappeared, 4th sound can be seen.

II. *Central Haemodynamic Findings*

1 *Pressure measurements*

The effects of amyl nitrite on the simultaneously measured pulmonary capillary venous, left ventricular end-diastolic and central aortic pressures in patients with isolated AI grades III and IV are summarized in Table 29. The systemic arterial pressure decreased markedly the systolic more than the diastolic. The maximal decrease occurred 30–50 sec after the start of the inhalation. The left ventricular end-diastolic pressure measured at the level of the post *a* wave also

Table 29 *Effect of amyl nitrite inhalation on left ventricular filling pressure and central aortic pressure*

HR heart rate, PCV – pulmonary capillary venous pressure, LV_{ED} left ventricular end-diastolic pressure ("post wave"), Ao aorta, Ao_D–LV_{ED} gradient – the end-diastolic gradient over the aortic orifice, M mean, S – systolic, D – diastolic

	Pressures, mmHg					
	HR (beats/min)	PCV (M)	LV_{ED}	Ao_S	Ao_D	Ao_D LV_{ED} gradient
Before inhalation						
Mean	73	8.7	10.0	143	59	50
S D	10.4	4.7	6.7	21.7	11.6	13.0
S E.M.	2.2	1.2	1.5	4.5	2.4	3.0
Peak effect of amyl nitrite						
Mean	99	5.8	2.9	99	48	44
S D	18.3	3.1	3.2	16.6	9.9	9.3
S E.M.	3.8	0.8	0.7	3.5	2.1	2.1
Change in percent	36	−33	−71	−30	−19	−12
	23	16	19	23	23	19
P	<0.001	<0.01	<0.001	<0.001	<0.001	<0.05

decreased in all cases and the decrease was considerable especially in patients with a greatly elevated LV_{ED}. The maximal pressure decrease noted was 21 mmHg (from 25 to 4 mmHg) The reduction of the PCV mean pressure *during the* inhalation was less pronounced on the other hand, and in some cases this pressure remained practically unchanged.

2. Flow measurements

As can be seen in Table 30 during the amyl nitrite inhalation there was a considerable increase in the effective forward flow simultaneous with the noted increase in heart rate The effective stroke volume also increased in all patients, though to a lesser extent this increase varied between 2 and 56 ml. Corresponding to the decrease in the systemic arterial pressure and the increase in the cardiac output, the total peripheral vascular resistance decreased greatly In the 6 patients in whom this could be calculated, this reduction amounted on the average, to 58 %

Table 30 *Effect of amyl nitrite inhalation on cardiac output* ($\dot{Q}_f$) *and stroke volume* (SV_f) *in patients with isolated AI grades III and IV*

HR = heart rate, Q_f = cardiac output (effective forward flow), SV_f = effective forward stroke volume

	HR (beats/min)	Q (L/min)	SV (ml)
Before inhalation			
Mean	68	5.86	87
S.D	8.4	1.28	21.1
S.E.M	2.7	0.41	6.7
Peak effect of amyl nitrite			
Mean	98	10.13	104
S.D	19.5	2.40	19.1
S.E.M	6.2	0.76	6.1
Increase in per cent	44	73	20
	10	10	10
p	< 0.001	< 0.001	< 0.01

DISCUSSION AND CONCLUSIONS

As mentioned previously in the introduction amyl nitrite inhalation causes peripheral vasodilatation which is manifested as flushing of the face neck and upper part of the trunk and as a decrease in the total peripheral resistance with an ensuing blood pressure reduction, and secondary to this both an increase in the heart rate induced in the baroreceptor mechanism (Goodman and Gilman 1965) and an increased venoconstriction (Mason and Braunwald 1965 Delius and Enghoff 1970). The increase in cardiac output in the patients of the present study is in agreement with the *findings in* normal persons by other authors (Beck et al. 1961 Perloff et al 1963 deLeon and Perloff 1966) These authors obtained no definite increase in stroke volume on the other hand such as was found in the present patients with AI.

In association with the decreased peripheral resistance and the hypotension during the inhalation, with consequent activation of the baroreceptor mechanism, the ejection of blood from LV is facilitated the decrease in LV filling pressure in these patients with AI is interpreted as a sign *of improved left ventricular function* and a reduced regurgitant volume The shortened diastole due to the tachycardia will probably also contribute to the decrease in the volume of regurgitating blood The mode of reaction described appears to agree with the findings that have been made in muscular exercise with its reduction of the peripheral resistance and its positively inotropic influences which contribute towards increasing the stroke volume The diminution of the regurgitation murmur noted on auscultation and phonocardiographically (cf Kahler 1933 Bourvaros and Lessof 196., Endrys and Bártová 1962) and the augmentation of the systolic ejection murmur during amyl nitrite inhalation agree with the findings in the pressure and flow determinations described.

In the present study a decrease in the amplitude of the *AI murmur* during amyl nitrite inhalation was observed in 87 % of the patients. The corresponding figure reported by Wrabec et al. (1971) for patients with AI combined with MS was 71 %

As an objective criterion of a definite haemodynamic effect of amyl nitrite, Richter et al. (1967) give a heart rate increase of more than 10 beats per min. In one of the patients of the present study in whom the amplitude of the murmur did not decrease during the inhalation the heart rate increase during the inhalation was only 8 beats per min. No definite explanation for the absence of a reaction of the murmur in the other 4 patients can be given. There was neither high age with its reduc reaction capacity of

the circulatory system, nor decompensation, which two alternatives have been suggested by Richter et al. (1967) as plausible explanations for a lack of reaction.

With regard to the presystolic rumbling murmur described by Austin Flint in 1862 the *Austin Flint murmur* which he found in two patients with AI and left ventricular dilatation opinions are divided both as to its origin and to its timing in diastole (presystolic and/or mid-diastolic)

In agreement with Austin Flint, Lunsada (1950) considered that the rumbling diastolic murmur was due to relative mitral stenosis and was caused by the vibrations that occur on the passage of blood through a mitral ostium of normal width with an enlarged left ventricle. Parker et al. (1971) found a significant relationship between the Austin Flint murmur on the one hand and the regurgitant volume and left ventricular stroke volume, on the other In most of these cases they found an elevated left ventricular end-diastolic pressure (on the average 24 mmHg) which is in good agreement with the findings in the present patients with a low-frequency apical presystolic murmur These authors assume that both the mid-diastolic and presystolic murmurs observed in most cases are caused by antegrade flow through a partially open valve.

But the theory most commonly put forward is that the regurgitant blood stream from the aorta forces the anterior aortic leaflet of the mitral valve upwards towards the mitral ostium and thereby produces a functional mitral stenosis (Segal et al. 1958 Ueda et al. 1965 among others) This is doubted, however by Loogen et al. (1965) who believe that the murmur arises from turbulence caused by the blood regurgitating to the left ventricle.

Currens et al. (1953) McKusick (1958) and Ross & Criley (1964) consider that the best explanation for this Austin Flint murmur is the occurrence of vibrations of the aortic leaflet of the mitral valve produced by the interaction of two blood streams entering LV during diastole one from the aorta and the other from the left atrium The oscillation of this leaflet between the two streams has been demonstrated angiocardiographically by Ross and Criley (1964)

According to Lochaya et al. (1967) and O'Brien and Cohen (1969) in severe AI with a reversed pressure gradient over the mitral ostium at the end of diastole the occurrence of turbulent flow at the mitral ostium and possible diastolic MI which has been shown angiocardiographically by the former authors, might be the cause of the murmur

Thus there is no unanimous explanation for the occurrence of this murmur

Conclusions. Amyl nitrite given in a dose which causes a sufficiently large reduction of the systemic arterial pressure with a secondary increase in the heart rate produces an improvement of the left ventricular function in patients with AI by increasing the outflow of blood from LV and decreasing the regurgitant volume All 5 patients with a low-frequency diastolic crescendo murmur over the apex of the type usually called an Austin Flint murmur had severe AI with an elevated left ventricular end-diastolic pressure. During amyl nitrite inhalation the presystolic murmur disappeared almost completely and both the LV_{en} and PCV mean pressures became normal—in contrast to the finding in organic mitral stenosis (Beck et al 1962, Kiger 1963 Endrys et al 1964)

VII ANGIOCARDIOGRAPHIC EXAMINATIONS

Angiocardiographic methods and correlations with some clinical and haemodynamic findings

In collaboration with Lars Björk, M.D

Through the development in thoracic surgery and the increased possibilities of surgical treatment of congenital and acquired heart diseases, the methods of angiocardiographic examination have come to play an important role as a part of the preoperative evaluation of these patients. During the last decades different methods for selective left heart angiocardiography have been developed and have attained increased importance. By means of these radiological contrast examinations, anatomical changes in the mitral and aortic valves can thus be characterized in detail, consequent functional alterations can be assessed and volume calculations for the left atrium and ventricle can be made.

With the aid of thoracic aortography the diagnosis in patients with suspected aortic incompetence can be established in a relatively simple and risk-free way and a semiquantitative measure of the degree of severity can be obtained. This method has therefore become generally accepted, and in our hospital as in many other places it has come into routine use in the evaluation of these patients. The diagnostic value of the method is perhaps most marked in those cases of aortic incompetence where the clinical findings are particularly difficult to assess, as for example in combination with other valvular diseases (Runco et al. 1961, Segal et al. 1964, Cohn et al. 1967, among others) or in congestive heart failure (Gorlin and Goodale 1956). But in other cases also a discrepancy may sometimes occur between the degree of severity assessed from clinical and haemodynamic findings and that assessed from the angiographic picture (Jefferson 1960, Frank et al. 1965, Demany and Zimmerman 1966, Cohn et al. 1967). Furthermore, as reported by Barrett et al. (1964), in routine investigations with thoracic aortography the presence of an unexpected aneurysmatic dilatation of the aortic root can be revealed in patients with aortic incompetence; this is of importance especially from an operative aspect.

METHODS

Review of the Methodological Development in Selective Left Heart Angiocardiography

Thoracic aortography

In 1939 Castellanos and Pereiras described the first attempt at retrograde (counter-current) aortography in man after injection of a contrast agent into a peripheral artery; these investigations were made on children. Thoracic aortography by injection of contrast material directly into the ascending aorta via a catheter advanced through the radial artery was introduced in 1947 by Radner (1948). He obtained good opacification in the thoracic aorta, in both children and adults. This technique was developed further by Brodén et al. (1948) and Jonsson et al. (1949 and 1951). The introduction of the percutaneous catheterization technique described by Seldinger (1953) has facilitated these examinations considerably (Ödman 1956, Ödman and Philipson 1958, Porstmann and Geissler 1959, Sutton 1960, Aker et al. 1964).

As early as in 1953 Castellanos and García, in an aortographic study of aortic incompetence performed on both living patients and autopsy cases, gave their express opinion that retrograde aortography is of decisive importance for the diagnosis of aortic incompetence. According to these authors Bustamente, Pérez, Stable, Guerra and Milanés had previously shown—the first to do so—a case of aortic incompetence on a roentgenogram showing regurgitation of contrast medium to the left ventricle in thoracic aortography but without any comments. The detailed account

made by Ödman and Philipson (1958) of their findings in aortic valve diseases made by thoracic aortography was followed by a large number of investigations which further confirmed the value of this examination, performed both alone (Nelson et al. 1958, Porstmann and Geissler 1959 Jefferson 1960, Steiner and Hollman 1962, Hansen and Davidsen 1964 Sellers et al. 1964 Frank et al 1965) and in combination with left ventricular angiography (Johnson et al. 1957 Amplatz et al 1961 Björk et al. 1961 Kjellberg et al. 1961 Aker et al. 1964 Cullhed 1964 Figley 1964 Taubman et al. 1966) Owing to the cineangiographic technique, the evaluation of the movements of the valves has been further improved (Jefferson 1960 Lehman et al. 1962, Klatte et al. 1962, Raftery 1965 and Eie 1970) as well as the assessment of the regurgitation in aortic incompetence (Lehman et al. 1962, Eie 1970 and others).

Many investigators have attempted to obtain a *semiquantitative measure of the degree of severity of the aortic incompetence* by evaluating, in different ways, the regurgitation of contrast material to the left ventricle in thoracic aortography Ödman and Philipson (1958) considered the following three factors to be of importance in the evaluation of the degree of incompetence firstly the rate at which the left ventricle is filled during the injection of contrast medium, secondly the time for which the contrast medium remains in the left ventricle and aorta after the end of the injection and thirdly the degree of dilatation and the emptying capacity of the left ventricle The same opinion was held by Kjellberg and co-workers in 1961 they divided aortic incompetence into two groups, one clinically insignificant with slight leakage insufficient to fill the left ventricle in diastole, and one clinically significant with such a large degree of regurgitation to the left ventricle that this is filled with contrast medium during diastole A classification into three grades was made by N lson et l. (1958) on the basis of the diastolic reflux of the contrast material to the left entricle (minimal, moderate and ad anced AI) and a simila classification was made later by Eie (1970) in his comparative haemodynamic and cineangiographic studies of aortic alve diseases Several investigators have gone one step further and used the gradation scale + to + + + + according to the rapidity of reflux and the degree of opacification of the left entricle (Runco et al 1961 Lehman et al. 1962 Sellers et al 1964 Cullhed 1964 Frank et al 1965 Cohn et al 1967)

In their report of the findings at thoracic aortography in aortic al e diseases, Ödman and Philipson (1958) also mention for aortic incompetence characteristic *morphological features in th aorta*, such as dilatation of the aortic sinus and the whole thoracic aorta and greater cyclic calibre variations than in normal persons, which has also been confirmed by Klatte et al (1962) Lehman et al (1962) and Thurn (1965) among others

Angiocardiography of the left heart chambers

In examinations of patients with aortic alve disease, complementation of thoracic aortography with *retrograde left ventricular angiography* can often, in a simple way gi further aluable information on the alve anatomy and structural changes and volume variations of the left ventricle (Johnson et al. 1957 Proton et al. 1957 Porstmann et al. 1958 Hanson et al. 1959 Amplatz et al. 1961 Steiner and Hollman 1962, Aker et al 1964 Sellers et al. 1964). Most of these authors have shown, in addition, that by means of the left entricular injection it is also possible to evaluate any concurrent mitral incompetence. The importance of ventriculography for establishing regurgitation to the left atrium had already been demonstrated earlier in connection with puncture of the left ventricle by Núñez and Ponsdomenech (1951) Smith et al. (1956) and others, and after these authors also by Björk and Lodin (1959) Kjellberg et al. (1961) and Malers (1964) Several of the authors mentioned previously (Porstmann et al. 1958 Amplatz et al. 1961 Aker et al. 1964 Sellers et al. 1964) have also expressed their opinion that retrograde catheterization of the left entricle with injection of contrast medium both into the ascending aorta and into the left entricle, is the most suitable and most informative method of examination in aortic incompetence suspected to be combined with mitral incompetence. In pronounced aortic incompetence with opacification of the entire left entricle concurrent mitral incompetence (primary or secondary) can be diagnosed from thoracic aortography by regurgitation of contrast medium to the left atrium, which has been observed by Philipson and Ödman (1958) and Figley (1964) among others, and also as early as in 1953 by

Castellanos and Garcia, which latter authors also succeeded in reproducing this finding post mortem. Because of the reduced risk of arrhythmias in injection of contrast material into the ascending aorta, Taubman et al. (1966) considered that under these conditions mentioned above a more reliable evaluation of the mitral incompetence is obtained and also a more physiological state for calculation of left ventricular volumes.

As in aortic incompetence, the cine method has been considered to give better information on the valvular function in mitral incompetence than full-size angiography (e.g. Khalaf et al. 196_) and to facilitate the assessment of functional mitral incompetence caused by ventricular arrhythmia (Figley 1964). Honey et al. (1969), however, in their thorough, critical study of 137 cineangiocardiograms in mitral incompetence point out the difficulties and sources of error in this method with regard to evaluation of the degree of incompetence, and consider it necessary to correlate the angiocardiographic results with the clinical and haemodynamic findings.

The *transseptal technique* can be used with advantage for injection of contrast medium into the left ventricle or left atrium in cases where it is difficult to pass through the aortic ostium the retrograde way as in a narrow aortic stenosis or a greatly dilated ascending aorta, or where there are other indications for transseptal catheterization (Brockenbrough and Braunwald 1960, Beuren and Apitz 196_, Braunwald et al. 196_, Endrys and Steinhart 1962, Paulin and Varnauskas 196_, Beuren and Apitz 1963). In the evaluation of possible mitral incompetence this method is less suitable since in the presence of a rigid catheter in the mitral ostium there is some risk of artificial regurgitation (Paulin and Varnauskas 1962, Honey et al. 1969). For determination of the end-systolic and end-diastolic volumes of the left ventricle, we have preferred to inject the contrast medium into the left atrium in order to avoid ventricular arrhythmia which renders the volume calculations difficult (Fleming and Hamer 1965, Engholf and Culhed 1971).

Methods for measurement of the left ventricular volume in biplane full-size angiocardiography in man were introduced by Dodge and co-workers (1956, 1960) and Arvidsson (1958, 1961). Comparative studies of systolic and diastolic volumes of the left ventricle calculated from biplane and single plane angiograms have been carried out by several investigators, including Hawley et al. (1965) and Sandler et al. (1968). Such good agreement was obtained in these studies that the single plane technique has been considered applicable for volume measurement by means of cineangiography (Greene et al. 1967, Kasser and Kennedy 1969, Hammer and Björk 1969). The introduction of this latter method, with its rapid exposure rate, constitutes a clear step forward in the study of the functional capacity of the left ventricle by construction of volume curves and pressure-volume curves (Chapman et al. 1958, Gribbe et al. 1959, Rackley et al. 1967, Björk 1970). Several cineangiographic model studies have been conducted for calculation of the true volumes of the left ventricle in animals (Chapman et al. 1958, Gribbe et al. 1959, among others) and in man (Rackley et al. 1967, Bruns 1970). Model investigations with full-size angiography have been performed by Sanmarco and Bartle (1964) among others, in animals and man and in large series with 5–8 different mathematical models by Sanmarco and Bartle (1966) in animals and by Dodge and Sandler (1960) and Davila and Sanmarco (1966) in man. Direct comparisons have also been made between left ventricular volumes determined by means of angiocardiography and methods for thermodilution (Sanmarco and Bartle 1964, Bartle and Sanmarco 1966 *a* and *b*), dye dilution (Frank et al. 1971) and fiberoptic dye dilution (Hugenholtz et al. 1968) and ascorbic acid (Carleton et al. 1966). Further tests of the validity and accuracy of angiographic volume determinations have been made in the form of comparative studies between the stroke volume, determined by means of angiography and according to the Fick principle (Arvidsson 1961, Dodge et al. 1962, Pech and Porstmann 1965) and the dye dilution technique (Hay et al. 1961, Dodge et al. 1962, Miller and Swan 1964 and Bartle and Sanmarco 1966 *a*). These studies were performed on persons with no signs of valvular incompetence or shunt.

In order to obtain a *quantitative measure of the degree of aortic incompetence* attempts have been made in a number of cases to determine the regurgitant volume by subtracting the effective stroke volume, determined either by the Fick method (Arvidsson and Karnell 1964, Sandler et al. 1963) or by the dye dilution technique (Sand-

ler et al. 1963) from the total stroke volume (the difference between the end-diastolic and the end systolic volume of the left ventricle) calculated by means of angiocardiography

Own Investigations

For the angiocardiographic investigations both the retrograde and the transseptal catheterization approach were used for injection of contrast medium into the ascending aorta, left ventricle and left atrium.

I. *Thoracic aortography* was performed on all 81 patients, altogether 109 times, 15 times in the form of full-size angiography mainly during the first 1½ years of the investigation period, and 94 times in the form of cineangiography; in 1 patients aortography was performed by both methods, and in 16 patients duplicate cineangiographies were performed.

II. *Retrograde left ventricular angiography* was performed altogether 25 times on 23 patients, mainly for exclusion of possible mitral incompetence 8 times in the form of full-size angiography and 17 times as cineangiography; in 2 examinations both methods were used.

III. *Transseptal left atrial angiography* was performed altogether 59 times on 57 patients for calculation of end-diastolic and end-systolic left ventricular volumes, 53 times in the form of full-size angiography and 6 times as cineangiography; in 2 examinations both methods were used. In one patient with suspected mitral incompetence, in whom an attempt to reach the left ventricle retrogradely was unsuccessful, contrast medium was injected into the left ventricle through the transseptal catheter

The angiographic technique

The above roentgenological contrast examinations, for which no anaesthesia and no special premedication were given, were performed as a termination of the haemodynamic studies. Immediately before the injection of contrast medium the patients were asked to take a deep breath and then to hold their breath throughout the exposure time but to avoid a Valsalva manoeuvre. In cases where contrast material was injected into the ascending aorta the tip of the catheter was placed 1–2 cm above the aortic valvular plane in order to obtain optimal conditions for evaluation of the degree of incompetence (cf also Eie 1970)

The contrast medium used in most cases was 60 Isopaque[1] (in a few cases at the beginning of the investigation series 76% Urografin®[2] was used) which was injected in a dose of 50–55 ml by means of an automatic high-pressure syringe by the method of Gidlund (1956) the pressure was 5–6 kg cm for injection into the ascending aorta or lower and 3–3 5 kg cm² for injection into the atrium or ventricle the lower pressure was used in the latter cases in an attempt to reduce movements of the catheter and consequent extrasystoles, during the injection of contrast medium The injection rate was about 20–30 ml/sec The exposures were begun immediately after the start of the injection of contrast medium, with a maximal delay of 0 1 sec No ECG triggering was used

The filming was performed by two different methods—biplane full-size radiography and cineradiography In the former method a two-plane roll film changer (Elema Schönander[3]) and a triple angiomatic apparatus with exposure factors of 800 mA and 60–80 kV were used. The duration of each exposure was 0 04 sec. The film-focus distance was 90 cm. The patients were placed in the supine position. The exposures were made simultaneously in two planes with a frequency of 6 frames per sec for 3 sec and then 1 frame per sec for 10 sec. In left ventricular angiography true frontal and lateral projections were used During thoracic aortography the patient was examined in the left anterior oblique position (left side rotated upwards) (Ödman and Philipson 1958) The cineangiographic filming was performed in one plane with the patient in the supine position, generally with the right side rotated upwards towards the image intensifier (right anterior oblique position) but in a few cases with the left side rotated upwards (left anterior oblique position). For this a 9-inch image intensifier and a 35 mm film camera (Arriflex) were used. The exposure rate was 40 frames per sec, the duration of each cine pulse was 0.003 sec and the remaining exposure data were 320 mA

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[1] 0.528 g sodium metrizoate, 0.028 g calcium metrizoate, 0 02 g magnesium metrizoate and 0 03 g methylglucamine metrizoate per ml, Nyegaard & Co A/S, Oslo, Norway

[2] 0 66 g methylglucamine diatrizoate and 0.1 g sodium diatrizoate per ml, Schering AG, Berlin, Germany

[3] Elema-Schönander Ltd., Stockholm, Sweden.

and 50–70 kV Geometrical magnification with a magnification factor of 1 3–1 8 was generally used. In order to obtain a reference measure a ruler with mm grading was placed in the same plane as the left ventricle and recorded on the same film strip as the angiocardiogram, before or after the injection of contrast medium. During all roentgenological contrast examinations ECG was recorded continuously· in practically all cases the systemic arterial pressure was recorded and in most cases markings for injection and exposure. As in the previously described haemodynamic studies, a direct-writing four-channel or six-channel ECG apparatus (Mingograph 42 and 81[1] respectively) was used also for these recordings, and pressure measurements were made with pressure transducers EMT 34 and 35[1] and an EMT 31 electromanometer[1]

Methods of evaluation

1 Evaluation of the degree of aortic regurgitation (*a*) *Semiquantitative method. Classification of aortic incompetence on the basis of thoracic aortographic findings.* In this study the classification of the incompetence was based on the degree of contrast filling of the left ventricle on injection of contrast medium into the ascending aorta (Cullhed 1964) as used routinely in our clinic:

Grade I subvalvular reflux (Fig. 28)

Grade II. the upper half of the ventricle is filled with contrast medium (Fig. 29).

[1] Elema-Schonander Ltd., Stockholm, Sweden.

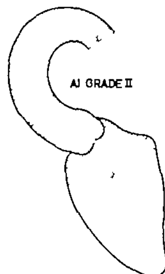


Fig 29

Grade III. the entire ventricle is filled with contrast medium but the contrast density is low considerably lower than in the ascending aorta (Fig. 30)

Grade IV as grade III, but the contrast density in the ventricle is similar to that in the aorta (Fig. 31)

In the present material an attempt was made to divide AI grade IV further into two sub-groups, namely $AI_{IV \geq 1s}$ and $AI_{IV<1s}$ according to the total diastolic filling time of the left ventricle with the boundary line placed at 1 sec. Thus in $AI_{IV \geq 1s}$ the filling time was equal to or more than 1 sec and

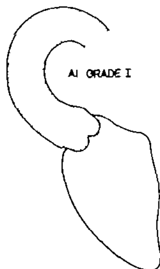


Fig 28

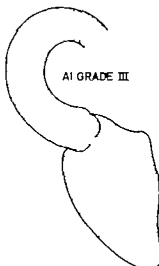


Fig 30

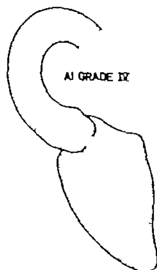


Fig. 31

in AI_{IV-3} less than 1 sec. In AI grade IV the filling time was counted as the total diastolic period from the start of the injection to the first film with the same contrast density in the ventricle as in the ascending aorta. In AI grade III the time required to obtain the first film with thin opacification of the entire ventricle was determined.

The total diastolic filling time was calculated from the arterial pressure curve which together with the ECG was recorded continuously during the thoracic aortography with a paper speed of 100 mm/sec, rendering possible an evaluation of the time in secs. Since an effect of the injection rate on the filling time cannot be excluded, only those cases were included where the rate of injection varied between 23 and 31 ml/sec. These limit values comprised the mean value (26.8 ml/sec) ± one standard deviation (3.8 ml/sec = 14%) which were calculated from 50 thoracic aortographies (range 16–33 ml/sec). The median was 28, the lower quartile 24 and the upper quartile 29 ml/sec, which values can be considered to agree approximately with the values given above.

(b) Quantitative method. Determination of the regurgitant volume with a combination of the angiographic and dye dilution technique. As mentioned previously in this chapter the difference between the total and the effective stroke volume constitutes a measure of the regurgitant volume. The total stroke volume of the left ventricle was calculated in the angiographic technique by subtracting the end-systolic from the end-diastolic volume. The effective stroke volume was determined by means of the dye dilution method, mostly with duplicate determinations, with injection of the dye into the superior vena cava or the right atrium and collection of blood from the brachial artery (for further details of the dye dilution technique reference may be made to "Methods" in the chapter on haemodynamic studies). In order to obtain the determinations of the effective and the total stroke volume in as rapid a sequence and under as similar external conditions as possible the dye dilution curves were not recorded until the patient had been placed in position for the contrast examination. The injection of contrast medium was started as soon as possible within 1–2 min after the determination of the effective flow had been completed. With the exception of two cases, at these examinations the left ventricular volumes were calculated from full-size angiograms.

In comparative investigations of patients who had had no valvular incompetence or shunt, it was found that the values for the stroke volumes determined angiographically were higher than the corresponding values obtained by the Fick method (Gribbe 1960, Dodge et al. 1962) or the dye dilution technique (Dodge et al. 1962, Miller and Swan 1964). For this reason before calculation of the regurgitant volume all angiographically measured stroke volumes were corrected by an empirically obtained factor, one for each angiographic method. In 9 patients (7 with aortic stenosis and 2 with mitral stenosis) the stroke volume calculated from full-size angiograms was compared with the corresponding value obtained according to the Fick principle. On calculation of the regression line through the origin the coefficient 0.41 was obtained for conversion of the value for the angiographic volume to the corresponding Fick value. In 4 of the patients the angiographic stroke volume could also be compared with the corresponding value determined by the dye dilution technique, whereby the factor was calculated to be 0.4. When all 13 values were used as a basis for the calculation the correction factor 0.4 was obtained (Fig. 3).

It was considered most correct to calculate the linear regression through the origin especially since the material upon which the calculation was

based was relatively small and showed fairly large deviations. When each Fick value and dye dilution value, respectively was expressed in per cent of the corresponding angiographic value a mean value of 42 ± 2.9% (Mean ± S.E.M.) was obtained when the calculation was based on the 9 Fick values, and 42 ± 2.4% when the combined Fick and dye dilution values were used as a basis.

There was no significant difference in the heart rate at the time point for the stroke volume determination by the Fick and angiographic methods; the mean difference was 0.2 ± 3.1 beats/min ($\bar{d}$ ± S.E.M.). In the 4 patients in whom the stroke volume was determined by the Fick method and also some hours later by the dye dilution technique, no significant difference was found between the values obtained by these two methods; the mean difference was 0.25 ± 5.6 ml ($\bar{d}$ ± S.E.M.)

A correction factor was calculated also for the cineangiographic method by comparison between the stroke volumes determined angiographically and according to the Fick principle. The study was performed on 7 patients without valvular incompetence or shunt (6 patients with angina pectoris but without myocardial infarction and 1 patient with a previous acute myocarditis). Calculation of the linear regression through the origin showed the Fick value to be 70% of the angiographic value. The difference in heart rate at the time of the stroke volume determination between the Fick method and angiocardiography was higher in this study but not significant, the mean difference was 6.1 ± 2.6 beats/min.

2. Methods for estimation of left ventricular volumes

The volumes of the left ventricle were calculated by two methods.

(*a*) *Biplane full size angiocardiography* For calculation of the left ventricular volumes from biplane, full-size angiocardiograms the method described by Arvidsson (1958 1961) in which the chamber is assumed to be an ellipsoid and both axes are measured directly on the film was followed essentially. Approximately half the thickness of the trabecular network visible in diastole was included in the measurements. An attempt was made as far as possible to make the volume determinations during cardiac cycles free from arrhythmia in the form of extrasystoles with compensatory pauses.

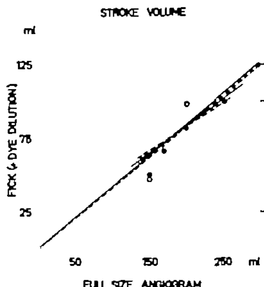


Fig. 32 Relationship between stroke volume (in ml) determined by full-size angiography and that determined *either* ( ) by the direct Fick method (filled circles) in 7 patients with pure aortic stenosis and 2 patients with pure mitral stenosis, *or* (*b*) by the dye dilution technique (open circles) in 4 of these patients. The best straight regression line through the origin for (*a*) was $y = 0.41\ x$ (S.D. = 18.1) and for (*a* + *b*) $y = 0.42$ (S.D. = 17.1); the best straight regression line not drawn through the origin for (*a*) was $y = 18.6 + 0.32$ (S.D. = 18.7) and for (*a* + *b*) $y = 11.1 + 0.36$ (S.D. = 17.7).

(b) *Single plane cineangiocardiography* For calculation of left ventricular volumes from *single plane cineangiocardiograms* we have used since the latter half of 1968 in routine left heart catheterizations, a technique for computer analysis of left ventricular volumes and also pressure data. The method has been described in detail by Björk (1970). During the angiographic examination arterial and left ventricular pressures are recorded in addition to ECG allowing a construction of pressure-volume curves. The construction of the volume curves is semi-automatic and comprises several stages: the cinefilm is projected, with considerable magnification, onto a transparent screen with an inbuilt coordinate system, from which the coordinates required for calculation of the left ventricular volumes are obtained by following manually the contour of the ventricle: the coordinate values are then fed to a computer via a tape. At least two consecutive cardiac cycles are generally recorded, and an attempt is made to avoid arrhythmic cycles. For calculation of the left ventricular volumes

the mathematical formula $V = \pi LD^2/6$ is used, where V = the volume of the left ventricle L = the longest diameter of the projected area and $D = 4A/\pi L$, where A = the projected area (see also Davila and Sammarco 1966)

3. Thickness of left ventricular wall

This was measured in diastole approximately half-way between the apex and the base, mostly on full-size angiograms—in these cases in the frontal plane—but in a small number of cases on cineangiograms.

In full-size angiographic examinations the *diameter of the aorta* was measured at the end of systole and diastole, generally on the films taken in the lateral projection, measurements being made both of the ascending aorta at the position of the aortic valve annulus, and of the descending aorta at the same level.

RESULTS

I. *Left Ventricular Volumes*

The end-systolic (ESV) and end-diastolic (EDV) volumes of the left ventricle were calculated from *biplane full-size angiograms* in a total of 54 patients—with injection of contrast medium into the left atrium in 48 patients, retrogradely into the left ventricle in 5 patients and into the ascending aorta in 1 patient—and from *cineangiograms* in a total of 21 patients with contrast injection into the left atrium in 6 patients and into the ascending aorta in 15 patients. In 7 patients both methods were used at the same examination for the volume calculations.

1. *Technical and haemodynamic factors influencing the volume measurement*

(*a*) *Technical factors* rendered determination of the left ventricular volumes impossible in 8 cases. Of these, the film quality was too poor in 5 cases—4 cases of full-size angiograms and 1 cine angiogram. In 2 cases the opacification was too poor due to the fact in one case that the transseptal catheter recoiled from the left atrium to the right during the contrast injection, and in the other case, also during the injection that the retrograde catheter recoiled from the left ventricle to the aorta. In the 7th patient the contrast examination had to be abandoned because of coagulation in the transseptal catheter

(*b*) *Haemodynamic factors* in the form of *arrhythmia* made the volume determinations in full size angiography difficult in several cases. Thus in left atrial angiography a predominantly supraventricular arrhythmia with 1–2, occasionally up to 3–4 supraventricular ectopic beats was noted in just over half of these examinations (in 31 patients) in 6 patients isolated ventricular extrasystoles were recorded, and the same was observed in 2 of the left ventricular injections and 3 of the aortic injections. During the cineangiographic examinations for determination of the left ventricular volumes isolated extrasystoles were noted in 5 patients, but these did not affect the volume measurements. One further patient, examined by the cine method showed arrhythmia in the form of atrial fibrillation with a ventricular frequency of about 70 beats/min. When the extrasystoles in full-size angiography appeared at the start of the injection or after its end they had no disturbing effect on the calculation of the left ventricular volumes, which generally took place (2.0)–5–3.5 sec after the start of the injection (angiographic film No. (12)–15–21) In the remaining cases with ectopic beats it was sometimes difficult to find films with good opacification at end-systole and end-diastole during completely arrhythmia-free cardiac cycles. Thus in 7 patients the ESV determination had to be made from films taken immediately after a compensatory pause and in 6 patients the EDV determination had to be made from films taken at the end of a compensatory pause.

In an attempt to obtain an approximate idea of the order of magnitude of the influence of the arrhythmias on the volume measurements by means of full-size angiography comparisons were made between the end-diastolic volumes at different durations of diastole. The duration of diastole was calculated from the arterial pressure curve. In several cases the value for EDV during a normal (arrhythmia-free) cardiac cycle could be compared with the value obtained during another arrhythmic, cardiac cycle, e.g. immediately before an extrasystole or during a compensatory pause. In most cases the difference obtained was insignificant, between 0 and 20 ml at an EDV of 300–430 ml, but up to 50 ml in one case with a large EDV of 900 ml. The intraindividual difference in the diastolic duration varied between 1 and 40 csec. In some patients with a long dura

tion of diastole after an extrasystole, calculation of EDV from the last two films during the same compensatory pause showed a difference of 30–50 ml between these values. The first, lower value which practically corresponded to the time for a normal diastole was considered to be the truest value in these cases. In 4 other cases it seemed most correct to use the mean of the last two EDV values. In those patients in whom ESV could not be measured except after extrasystoles with a compensatory pause, the difference between the diastolic and systolic pressure in the arterial pressure curve at the compensatory pause was 10–20 mmHg higher than in an ordinary cardiac cycle. No reliable comparison between ESV with and without influence of arrhythmia could be made.

2. *Full size angiographic estimations*

Fig. 33 and Table 31 summarize the values for *left ventricular volumes* calculated from *full-size angiograms*. As is evident from the table, with increasing degree of aortic incompetence there was a successive increase in the end-diastolic and end-systolic volumes of the left ventricle as well as in the stroke volume but the range of distribution within the groups was relatively wide.

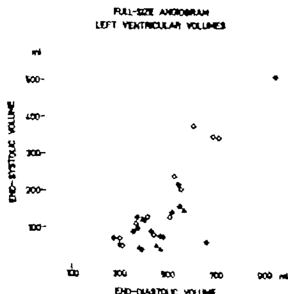


Fig. 33 End-systolic volumes in relation to end-diastolic volumes measured by full-size angiography in AI of varying degrees: grade I (cross), grade II (circles), grade III (triangles), grade IV (diamonds). The correlation coefficient between the end-diastolic and end-systolic volumes was = + 0.80 (95% confidence limits 0.67–0.88).

Table 31 *Left ventricular volumes determined by full-size angiography in 53 patients with aortic incompetence classified into grades I–IV on the basis of thoracic aortography and into the sub-groups $AI_{IV\geq 1s}$ and $AI_{IV<1s}$ according to the total diastolic filling time of the left ventricle*

EDV = end-diastolic volume, ESV = end-systolic volume, SV_t = total stroke volume

AI grade		Left ventricular volumes: EDV (ml)	ESV (ml)	SV_t (ml)	SV 0.42 (ml)
I		1	1	1	1
	Value	175	25	150	63
II		3	3	3	3
	Mean	255	70	185	78
	Range	165–300	50–110	115–250	48–105
III		9	9	9	9
	Mean	435	88	347	145
	S.D	124	56	100	42
	S.E.M.	41	19	33	14
	C.L. 95%	340–530	45–131	270–424	113–177
IV		40	40	40	40
	Mean	543	182	360	151
	S.D	184	128	113	48
	S.E.M	29	20	18	8
	C.L. 95%	486–599	143–222	325–395	137–166
IV ≥ 1s		10	10	10	10
	Mean	501	175	325	137
	S.D.	181	119	85	36
	S.E.M.	57	38	27	11
	C.L. 95%	371–630	90–260	265–386	111–162
IV < 1s		13	13	13	13
	Mean	614	201	404	170
	S.D	207	139	131	55
	S.E.M	57	39	36	15
	C.L. 95%	489–730	117–285	325–484	136–203
Differences					
$AI_{III}-AI_{II}$		9+3	9+3	9+3	9+3
	Mean	180	18	164	67
	S.E.M	61	27	68	22
	P	0.05	ns	<0.05	<0.05
$AI_{IV}-AI_{III}$		40+9	40+9	40+9	40+9
	Mean	108	94	13	6
	S.E.M	51	27	38	16
	P	ns	<0.05	ns	ns
$AI_{IV\geq 1s}-AI_{III}$		13+9	13+9	13 9	13+9
	Mean	179	113	57	25
	S.E.M.	71	43	49	21
	P	<0.05	0.05	ns	ns
$AI_{IV\geq 1s}-AI_{IV<1s}$		13+10	13+10	13+10	13+10
	Mean	113	26	79	33
	S.E.M.	81	54	45	19
	P	ns	ns	ns	ns

The results of comparison between the different grades of AI are difficult to evaluate since the groups varied in size and few observations were

made at the lower incompetence grades. There appeared, however to be a probably significant difference between AI grades III and II for EDV and SV_t, but between AI grades IV and III only for ESV On division of AI grade IV into the sub-groups $AI_{IV>1s}$ and $AI_{IV<1s}$ no significant difference was found between these two groups, but comparison between $AI_{IV<1s}$ and AI III showed that both EDV and ESV were probably significantly greater in group $AI_{IV<1s}$. For the sake of completion the values from the only patient with AI grade I were included, even though the volume measurements in this case were especially uncertain on account of arrhythmia with ventricular ectopic beats. From the comparative aspect, however they would seem to be of some interest.

In order to obtain, if possible, a more reliable measure both on comparison between the different grades of AI within this series of patients and on comparison with values of other investigators for normal persons and patients with AI the end-diastolic volume was also calculated in values related to the body surface area. The following mean values were obtained for the different grades of aortic incompetence given in Table 31 expressed in ml/m² body surface area with ranges or confidence limits at the 95% level: for grade I, 100; for grade II, 143 (range 109–165) for grade III, 246 (C.L. 204–288) for grade IV 291 (C.L. 260–321) for sub-group IV > 1s 267 (C.L. 186–347) and for sub-group IV < 1s 331 ml m (C.L. 264–398) As for the absolute values, these relative values also showed a probably significant difference between AI grades III and II and between $AI_{IV<1s}$ and AI III the mean differences were 103±25.2 and 85±35.6 ($\bar{d}$±S.E.M.) ml/m body surface area.

Fig. 33 shows both the distribution of the left ventricular volumes within the different grades of aortic incompetence, and the apparently relatively good linear correlation between the end-diastolic and end-systolic volumes apart from the patients with high end-systolic volumes the deviation in these cases may be interpreted as a sign of impaired left ventricular function The coefficient of correlation for all pairs of values is +0.80 (C.L. +0.67 to +0.88)

The left-ventricular end-diastolic volume in per cent of the total heart volume determined by the method of Jonsell (1939) lay within the limits for normal persons (18–33%) given by Björk and Lodin 1965) for AI grade I (27%) and AI grade II (32%) For the more pronounced grades of insufficiency this value was pathologically elevated for AI grade III the mean value was 43% (C.L. 36–51%) for AI grade IV 42% (C.L. 39–47%) and for the sub-groups $AI_{IV>1s}$ and $AI_{IV<1s}$ 38 (C.L. 31–45%) and 48% (C.L. 41–54%) respectively with a probably significant mean difference of 1% between these latter groups ($P < 0.05$)

On calculation of the *ejection fraction* (SV/EDV) which represents that part of the end-diastolic volume that is pumped out into the aorta during each systole and which can be used as an angiographic measure of the functional capacity of the left ventricle, the highest value 0.81±0.03 (mean ±S.E.M.) was found in the 9 patients with AI grade III and the lowest values in AI grade IV with negligible differences between the sub-groups and the total AI_{IV} group. The ejection fraction was thus 0.70±0.04 for $AI_{IV>1s}$, 0.68±0.04 for $AI_{IV<1s}$ and 0.69±0.03 for the whole AI_{IV} group This whole group showed a probably significant difference from AI III the mean difference was −0.11±0.04 ($\bar{d}$±S.E.M.) and $P < 0.05$ For the patient with AI grade I and the patients with AI grade II the quotients SV/EDV were 0.70 and 0.72, respectively The difference between AI grades III and II was not significant Fig. 34 illustrates graphically the relationship between the total stroke volume of the left ventricle and the end-diastolic volume in the different grades of AI. The volume values corresponding to an ejection fraction below 0.60 are represented by filled symbols. Of the patients with such values the 5 patients in whom the end-diastolic volume was greater than 600 ml showed an elevated filling pressure for the left ventricle both at rest and during exercise, and a pronounced general enlargement of the heart with a total heart volume of about 1 400–2 000 ml, corresponding to about 800–1 000 ml/m² body surface area in 4 patients and just over 700 ml/m² in 1 patient. In only one of these patients did the case history include clear signs of left ventricular failure

3 *Cineangiographic estimations*

Values for *left ventricular volumes* calculated from *cineangiograms* are presented in Table 32,

from which one patient (No. 94) has been ex cluded since the end-diastolic volume was beyond the limits for true estimation with this angiographic method. As in the left ventricular volumes determined by full-size angiography a progressive increase of the volumes was found with increasing degree of regurgitation although the differences between the groups in these studies were less pronounced and in no case statistically significant. The 2 patients with a mild MI combined with AI of grade IV showed no appreciable difference in these volumes from patients with pure AI grade IV

When the end-diastolic volumes calculated by the cine method were related to the body surface area, the following mean values were obtained for the AI grades given in Table 32 expressed in ml/m² body surface area with ranges or con fidence limits at the 95% level. for grade II 79 (range 72–86) for grade III 139 (range 75–196) and for grade IV 170 (C.L. 125–216) Calculation of the ejection fraction for the AI grades given in the tables gave the following mean values: 0.78 for grade II 0 66 for grade III and 0 62 ± 0 05 (mean ± S E.M) for grade IV

The linear relationship between the end-systolic

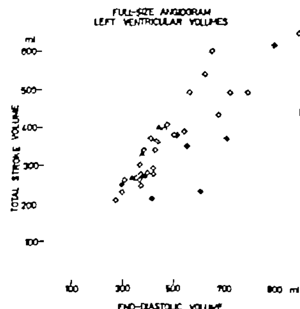


Fig. 34 Total stroke volume in relation to end-diastolic volume measured by full-size angiography in AI of varying degrees: grade I (cross)· grade II (circles) grade III (triangles)· grade IV (diamonds) Filled symbols ejection fraction below 0.60.

Table 32. *Left ventricular volumes determined by cineangiography in 18 patients with aortic incompetence classified into grades II IV on the basis of thoracic aortography and 2 further patients with aortic incompetence of grade IV combined with mitral incompetence of a slight degree*

EDV = end-diastolic volume, ESV = end-systolic volume, SV_t = total stroke volume

AI grade		Left ventricular volumes EDV (ml)	ESV (ml)	SV_t (ml)	SV (ml) 0.70
II		2	2	2	2
	Mean	140	30	110	77
	Range	130–150	25–35	95–125	67–88
III	n	4	4	4	4
	Mean	260	85	175	123
	Range	150–380	40–165	80–315	56–221
IV		12	12	12	12
	Mean	313	140	181	127
	S.D	127	108	48	34
	S E.M	37	30	14	10
	C.L. 95 ‰	232 394	75–205	151 212	106–148
IV + MI		2	2	2	2
	Mean	315	100	215	151
	Range	270–360	60–140	210–220	147 154

The differences between the mean volumes for the different grades of AI are not significant.

and end-diastolic volumes as determined from cineangiograms (Fig 35) is even clearer than that between volumes obtained from full-size angiograms (Fig. 33) but this cineangiographic study includes fewer patients with a history of left ventricular failure The correlation coefficient for these cases is +0.88 (C.L. +0.68 to 0.96)

4 Comparison between the full size angiographic and cineangiographic estimations

The results are presented in Fig. 36 and Table 33 In 7 cases of aortic incompetence a comparison could be made between values for the end-systolic and end-diastolic volumes of the left ventricle calculated from full-size angiograms and from cineangiograms. In these cases the patients were examined by both methods on the same day with an interval of about half an hour The cineangiography happened by chance, to be carried out first in all cases except one (No 80) The angiographies were performed under as similar conditions as possible however and as a basis of assessment of these conditions the heart rate and

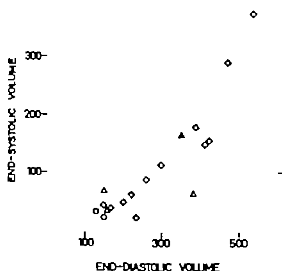


Fig. 35 End-systolic volume in relation to end-diastolic volume measured by cineangiography in AI of varying degree: grade II (circles)' grade III (triangles)' grade IV (diamonds). The correlation coefficient between the end-diastolic and end-systolic volumes was = +0.88 (95 confidence limits 0.68–0.96).

arterial pressures at the time of the olume measurements were used. The mean difference ($\bar{d}$ ± S.E.M.) between the full-size and cineangiographies was 5.9 ± 3 6 beats/min for the heart rate 21.2 ± 6.8 mmHg for the systolic arterial pressure and 2.3 ± 2.0 mmHg for the diastolic arterial pressure. In one patient (No 94) the end diastolic volume was much too large to be measurable with certainty by the cine method, and in another patient (No. 92) supraventricular extra systoles rendered determination of the end-systolic volume from full-size angiograms uncertain, and these volumes were therefore excluded. In our studies the cine recording showed considerably lower values throughout for the left entricular volumes than full-size angiography Thus the end-diastolic olume measured cineangiographically was, on the average, 64% of that calculated from full-size radiography and the corresponding value for both the end-systolic olume and the left entricular stroke olume was 61% (Table 33) A systematic difference was thus found between the methods, but the correlation between them for the end-systolic (= +0 996) and end-diastolic volumes (= +0 98) was good (Fig. 36) This was also evident in the good correlation found between the stroke volume obtained by the cine method and by full-size angiograph hen the evaluation was made both indirectly in two different materials by comparison of each method with the Fick method, and dire th in th d material by comparison between o umes al culated by the two methods Usin the p e mentioned correction factors 0.4 and 0 t conversion of the full-size olume (F cine-volumes (C) to correspond ng I k the equation

V_C 0 70 = V_{F-s} 0 42 is obtained, where I = volume.

5 *Thickness of left entricular all*

In the patient with AI grade I the thickness of the wall was 7 mm and in the 6 patients w th AI grade II 9.2 (range 8–11) mm. For the other two grades of AI the following mean alues (mean ± S.E.M.) and ranges were obtained: for AI grade III (n = 11) 11 9 ± 1 0 (8–20) mm and for AI grade IV (n = 55) 11 8 ± 0 3 (7–16) mm thus practically no difference.

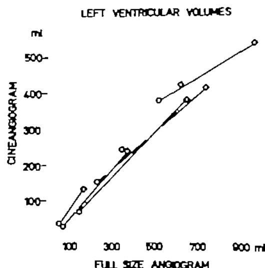


Fig 36 Comparisons between left ventricular olumes measured by full-size angiography and by cineangiography in 7 patients with aortic incompetence (see Table 33). Diamonds = end-diastolic volume (EDV); circles = end-systolic volume (ESV). The correlation coefficient between the two angiographic methods for EDV was = +0.98 (95% confidence limits 0.71 1.00), and for ESV = +0.996 (95% confidence limits 0 93–1.00)

II. *Regurgitant Volumes*

1 *Comparisons between the continuous infusion method and the combined angiographic and dye dilution technique*

In determination of the regurgitant volume, expressed in per cent of the total stroke volume it was possible in 5 patients to compare the results from continuous dye infusion with those obtained by full-size angiography combined with flow measurement by the dye dilution technique. No significant difference was found, the mean difference of the percentage values was 5.2 ± 3.9 and C.L. at the 95% level -2.5 to 1.9 According to Student's t test, $P = 0.60$ In 2 patients in whom the total stroke volume was determined by cine angiography a comparison could also be made between the two methods used in determination of the regurgitant volume. When the values thus obtained were included in the above calculations, $\bar{d}$ was -2.4 ± 5.7% and C.L. at the 95% level was -13.6 to 8.7 $P = 0.90$

2 *Comparisons between the regurgitant volume and the end-diastolic volume of the left ventricle*

(*a*) The relationship between the *left ventricular end-diastolic volume EDV* calculated from biplane *full size angiograms* and the *regurgitant volume* (i.e. the regurgitant fraction) expressed in per cent of the total flow can be seen in Fig. 37 The regurgitant volume was determined in 18 patients by the combined angiographic and dye dilution technique and in 8 patients by continuous dye infusion. In 4 of these 26 patients both methods were used. The coefficient of correlation between the regurgitant volume determined by the two respective methods, and EDV was calculated, and was found to be $+0.63$ (C.L. $+0.19$ to $+0.86$) with the combined angiographic and dye dilution technique and $+0.81$ (C.L. $+0.03$ to $+0.98$) with continuous dye infusion. The 5 patients with a regurgitant fraction of 65% or higher had considerable enlargement of the heart, with a heart volume of over 800 ml/m² body surface area and all except patient 94 (an 18-year-old boy) had an elevated filling pressure in the left ventricle during exercise of these

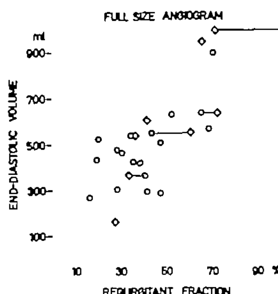


Fig 37 Relationship between the end-diastolic volume (measured by full-size angiography) and the regurgitant fraction (expressed in per cent of total flow). The regurgitant fraction is estimated by the combined angiographic and dye dilution techniques (circles) or by the continuous dye infusion method (diamonds). For the four patients in whom both methods were used for determination f the regurgitant fraction, the symbols re joined by line. The correlation coefficient between the end-diastolic volume and the regurgitant fraction for the combined angiographic and dye dilution techniques was $= +0.63$ (95% confidence limits 0.19–0.86), and for the continuous dye infusion method $= +0.81$ (95% confidence limits 0.03–0.98).

Table 33 *Comparisons between left ventricular volumes measured by full-size angiography and cineangiography*

The cineangiographic left ventricular volumes are given i per cent of the left ventricular volumes determined by full-size angiography In patient 92, the value of ESV obtained by full-size angiography was unreliable because of supraventricular arrythmia In patient 94 EDV was beyond the limits for true estimation with the cineangiographic method. EDV = end-diastolic volume, ESV = end-systolic volume, SV = total stroke volume

Patient No.	AI grade	$\frac{\text{Cineangiographic volume}}{\text{Full-size volume}}$ 100 EDV	ESV	SV
80	IV	64	36	70
81	IV	59	52	61
92	IV	69	—	—
94	IV	—	69	—
95	II	79	70	83
103	IV	56	74	36
104	IV	56	63	53
Mean		64	61	61
S.D		8.2	13.0	15.8
S.E.M.		3.7	5.8	7.9

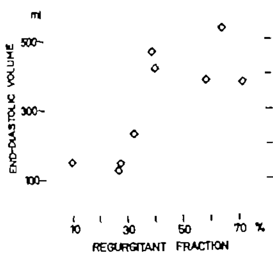


Fig. 38. Relationship between the end-diastolic volume (measured by cineangiography) and the regurgitant fraction (expressed as per cent of the total flow) estimated by the continuous dye infusion method, $r = +0.76$ (95% confidence limits 0.04–0.96).

5 patients, two (Nos. 67 and 81) also had a history of left ventricular failure. Patients 77 and 81 who were 58 and 59 years old, had in contrast to the other 3 patients, who were under 40 years of age, a low effective stroke volume of 50–55 ml during exercise.

(*b*) A comparison between the *regurgitant fraction* determined by means of *continuous dye infusion* and the *end-diastolic volume of the left ventricle* calculated from *single plane cineangiograms* was made in 9 patients (Fig. 38). A correlation was found between these values which showed very little difference from that with full-size angiography. The correlation coefficient in this study was +0.76 (C.L. +0.04 to +0.96).

III. *Grading of the Aortic Incompetence on the Basis of Thoracic Aortography*

The distribution of the patients into the four grades of incompetence which have been described under Methods of Evaluation earlier in this chapter can be seen in Table 1 in chapter I p. 12.

Duplicate examinations. In connection with the clinico-haemodynamic investigation of the 81 patients comprising this series, thoracic aortography was performed altogether 109 times, since these contrast examinations were carried out with both ful size a ogra hy ar a me 1 1 patients and with uplcat 1 16 patient O cca on r t e nat re cal one tle a h 1 be evalu ted h v du t 1 in 4 a s, to the fa that h t was located too high in 2 c ar in the form of ventricular e tr Of the remaining patient 5 s entricular extrasystoles in 4 c s ptal catheter lay in the left n aortography which may h rhythmia. This did not disturb the regurgitation howev r 1 a four bigeminal ventricular e tr s but not until after the contra ir ended and the grad of incompetence w th fore not affected.

In the 21 patients for whom the technical and haemodynamic conditions llowed an evaluation of the incompetence by duplicate determinations (in 12 cases with both full-size angiography and cineangiography and in 9 cases with duplicate cineangiographies) the examinations, except in 2 patients, were performed in succession with an interval of approximately 20–30 min. In these 2 patients left atrial angiography was performed between the duplicate examinations in question. According to the semiquantitati division into four grades of incompetence, one patient was classified as grade II, 6 patients as grade III and the remaining 14 patients as grade IV. The same result was obtained by both aortographies.

In 9 of these patients it was possible to study the *reproducibility in relation to the total diastolic filling time of the left ventricle* (Table 34) which meant a more precise gradation of the aortic incompetence which has been described previously in this chapter under Methods of Evaluation. The ECG and arterial pressure were recorded prior to and continuously during the aortographies. In 4 patients a comparison was made between cine (C) and full-size (*F s*) aortographies and in 5 patients between duplicate cineaortographies (C and C_2) at which latter examinations the projections differed in 2 patients (Nos. 40 and 65).

The diastolic filling time for the left ventricle varied between the first and second examination from 0.01 sec up to a maximum of 0.21 sec, without any systematic statistical difference. The mean difference in filling time between *C* and *F s*

was −0.01 sec and between C_1 and C_2 −0.06 sec. Neither of these differences was statistically significant, but any conclusion that may be drawn from these values is limited by the small number of observations in each group.

Every attempt was made to carry out the examinations under conditions as equivalent as possible as a basis of assessment of these conditions the heart rate the duration of diastole and the arterial blood pressure during the periods of contrast injection were used. As can be seen in Table 34 the mean difference between C and F-s and between C_1 and C_2 was not statistically significant either for the heart rate or for the length of diastole the scatter of the values was large. The same was valid for the arterial blood pressure. The mean difference between C and F-s was 2 mmHg (range +18 to −17) for the systolic and −9 mmHg (range −1 to −19) for the diastolic arterial blood pressure and between C and C_2 it was −14 mmHg (range +15 to −34) for the systolic and −7 mmHg (range +3 to −20) for the diastolic arterial blood pressure.

Classification according to filling time In 30 patients with AI grade IV and in 10 patients with AI grade III it was possible to calculate the total diastolic filling time for the left ventricle. In Table 35 the 30 patients with AI grade IV are ranked in order of magnitude of the filling time so that the first 17 patients with a filling time of less than 1 sec were assigned to the sub-group $AI_{IV<1}$ and the remaining 13 patients with a filling time over 1 sec to the sub-group $AI_{IV>1}$. This angiographic measure of the regurgitation was compared with other angiographic, haemodynamic and clinical findings, which partly constituted criteria of and partly influenced the evaluation of the degree of severity of the incompetence.

With regard to the *age distribution* in the two sub-groups, the mean age for group $AI_{IV>1}$ was 38.4 (18–60) years and for $AI_{IV<1}$ 43.6 (21–59) years.

Factors which may influence the angiographic evaluation of the degree of incompetence include among other things the *heart rate* the *duration of diastole* and the *volume of the ascending aorta*. The mean values for the heart rate and duration of diastole during the injection of contrast medium were 74.3 (53–110) beats/min and 0.53 (0.30–0.75) sec for sub-group $AI_{IV<1}$ and 63.7 (41–92) beats/min and 0.62 (0.40–0.75 1.02) sec for

Table 34 *Duplicate thoracic aortographies evaluated according to the total diastolic filling time of the left ventricle Comparisons between cineangiography (C) and full-size angiography (F–s) and between duplicate cineangiographies (C_1, C_2)*

Patient No.	AI grade	Angiographic method	Duri g injection period: Heart rate beats/min	Duration of diastole, sec	LV filling time sec
10	IV	C	68	0.59	0.91
		F-s	75	0.49	0.83
11	IV	C	100	0.35	0.80
		F-s	65	0.48	0.95
15	III	C	77	0.53	1.03
		F-s	65	0.60	1.00
39	IV	C	62	0.61	1.26
		F-s	58	0.70	[illegible]
40	IV	C_1	71	0.58	1.22
		C_2	67	0.53	1.21
65	III	C	70	0.50	1.36
		C_2	95	0.36	1.24
77	IV	C_1	74	0.49	0.64
		C_2	67	0.38	0.71
102	IV	C_1	63	0.57	0.45
		C_2	61	0.62	0.60
106	IV	C_1	68	0.60	0.66
		C_2	71	0.55	0.87

The difference in LV filling time between the means of C and F-s was −0.01 (range +0.01 to −0.15) sec, and between those of C_1 and C_2 −0.06 (range +0.01 to −0.21) sec. The differences were not significant, neither were the differences in heart rate and duration of diastole between the same groups.

$AI_{IV>1}$. In no case was the difference between the groups statistically significant.

Since it was not possible to determine the volume of the ascending aorta, the diameter at the annulus of the aortic valve had to be used instead as a comparative measure. In group $AI_{IV>1}$ several patients showed an *aneurysmally dilated ascending aorta* and a *wide annulus* with a diameter of 45.3 ± 2.68 mm (mean ± S.E.M.) in systole and 41.1 ± 2.81 mm in diastole. The corresponding values for group $AI_{IV<1}$ were 37.2 ± 1.55 and 33.2 ± 1.81 mm, respectively The mean difference between $AI_{IV>1}$ and $AI_{IV<1}$ was −8.1 ± 3.1 mm ($P < 0.01$) in systole and −7.9 ± 3.3 mm ($P < 0.05$) in diastole.

The values for the *left ventricular volumes* were somewhat higher in group $AI_{IV<1}$ than in $AI_{IV>1}$. On calculation from full-size angiography the

Table 35. Thirty patients with AI grade IV ranked in order of magnitude of the total diastolic filling time of the left ventricle as determined by thoracic aortography. This measure of the regurgitation is related to other findings at angiocardiography, dye dilution estimations and blood pressure values

Thoracic aortography was performed as cineangiography in all cases except patient No. 21, in whom full-size angiography was used. In patients 10 and 11 the LV filling time is the mean value from full-size and cineangiograms. Regurg. fract. = the regurgitant fraction of total flow; values in italics refer to combined angiographic and dye dilution techniques and the other values to the continuous dye infusion method. LV volumes: values in italics are cineangiographic volumes; the others are full-size angiographic volumes. Ao_D–LV_{ED} gradient = the end-diastolic gradient over the aortic orifice (Ao_D = aortic diastolic pressure; LV_{ED} = left ventricular end-diastolic pressure)

Pat. No.	Sex	Age (y)	During injection period: Heart rat (beats/min)	During injection period: Duration of diastole (sec)	LV filling time (sec)	Regurg. fract. (%)	LV volumes, ml: EDV	ESV	SV	Aortic annular diameter, mm: Systolic	Diastolic	Indirect blood pressure, mmHg: Diastolic	Amplitude	Direct aortic pressure, mmHg: Diastolic	Amplitude	Ao_D–LV_{ED} gradient (mmHg)
41	F	44	107	0.33	0.35		900	570	330	48	44	50–0	160	50	130	20
94	M	18	53	0.75	0.44	71	1 000	350	650	40	33	0	*160*	48	100	25
21	F	36	62	0.59	0.51		375	190	245	37	29	85–75	110	65	85	53
102	F	44	62	0.60	0.53	*59*	*385*	*180*	*205*			50–40	110	57	91	54
27	F	19	110	0.30	0.59		420	130	290	30	24	55–0	*160*	47	63	43
92	M	49	65	0.59	0.64	41	*420*	*155*	*265*	40	40	50–0	155	58	114	22
77	F	38	81	0.44	0.68	*68*	570	80	490	32	32	50–0	170	45	113	17
67	M	28	60	0.65	0.70	*70*	900	285	615	34	22	50–0	190	38	127	23
43	M	37	67	0.60	0.74		520	*140*	380	30	24	60–40	90	49	82	34
83	M	40	103	0.36	0.78	40	*470*	*290*	*180*	36	36	80	80	80	68	57
79	M	39	71	0.64	0.80		550	290	260	40	36	50–0	*165*	58	90	42
104	M	26	75	0.42	0.85		730	*240*	490	32	29	0	145	38	74	15
28	M	33	71	0.53	0.85		620	150	470	32	30	60–0	160	54	82	44
10	M	26	72	0.54	0.87					34	32	50–0	170	55	70	47
11	M	43	83	0.42	0.88		420	50	370	38	32	60–0	130	60	80	45
54	M	46	55	0.68	0.90		550	160	390	52	48	50–30	100	50	87	35
56	M	46	66	0.60	0.98		425	150	275	40	40	95	*105*	80	95	78
31	M	30	63	0.65	1.02		800	*310*	490	40	34	55–30	140	56	122	34
42	M	49	75	0.50	1.03		690	350	340	56		70–60	90	60	108	43
48	M	23	92	0.40	1.07	*16*	275	70	205	54	32	80–70	*55*	70	34	76
44	M	51	57	0.73	1.10		470	75	395	62	60	65	65	62	69	
57	F	35	63	0.58	1.17	*41*	300	70	230	40	36	65–45	70	58	66	76
76	M	21	60	0.65	1.20	*19*	440	80	360	48	44	65	65	64	42	64
40	M	43	69	0.57	1.22		370	110	260	48	44	85	90	61	85	41
98	M	35	63	0.62	1.25	*43*	260	90	*170*	Aneurysm		50–0	130	55	97	38
72	M	39	41	1.02	1.26	36	545	220	325	40	36	*60*	*100*	53	85	42
39	M	58	60	0.65	1.26		400	120	280	40	40	70–60	95	62	120	49
99	M	39	68	0.58	1.27		300	*115*	*185*			60–50	100	53	87	55
107	M	46	57	0.73	1.58		200	*50*	*150*	Aneurysm		*100–90*	90	85	60	74
32	M	58	60	0.70	1.66		715	345	370	45	44	70–60	100	37	84	28

Table 36. *Mean values and differences between means for indirect and direct blood pressure measurements in 10 patients with AI grade III and in 30 patients with AI grade IV classified into the two sub-groups* $AI_{IV>1s}$ *and* $AI_{IV<1s}$ *according to the total diastolic filling time of the left ventricle*

Ao_D = aortic diastolic pressure, LV_{ED} = left ventricular end-diastolic pressure

AI grade		Indirect blood pressure, mmHg Diastolic	Amplitude	Direct aortic pressure, mmHg Diastolic	Amplitude	$Ao_D - LV_{ED}$ gradient (mmHg)
AI_{III}	*n*	10	10	10	10	9
	Mean	67	91	69	76	62
	S.D.	29	38	11	14	14
	S.E.M.	9.0	11.9	3.5	4.3	4.7
$AI_{IV>1s}$		13	13	13	13	1
	Mean	57	92	60	81	52
	S.D	23	24	11	27	17
	S.E.M.	6.4	6.8	3.0	7.5	4.9
$AI_{IV<1s}$		17	17	17	17	17
	Mean	21	139	55	91	39
	S.D.	33	33	12	20	17
	S.E.M	8.0	8.0	2.9	4.8	4.1
Differences						
$AI_{IV>1s}-AI_{III}$		13+10	13+10	13+10	13+10	12+9
	Mean	−10	1	−9	5	−10
	S.E.M	11.1	13.7	4.6	8.6	6.8
	P	ns	ns	ns	ns	ns
$AI_{IV<1s}-AI_{III}$		17+10	17+10	17+10	17+10	17+9
	Mean	−46	48	−14	15	−23
	S.E.M	12.1	14.4	4.6	6.4	6.2
	P	<0.01	<0.01	<0.01	~0.05	<0.01
$AI_{IV<1s}-AI_{IV>1s}$	*n*	17+13	17+13	17+13	17+13	17+12
	Mean	−36	47	−5	10	−13
	S.E.M	10.3	10.6	4.2	8.9	6.4
	P	<0.01	<0.001	ns	ns	~0.05

mean difference for EDV was 113 ml, for ESV 26 ml and for SV 79 ml, but none of these differences is *statistically significant (see also Table 35).* Using the cine method, somewhat greater mean differences were obtained between the groups for EDV and ESV with values of 172 and 123 ml, respectively but the stroke volume difference was only 48 ml. In this case the number of observations was too small ($n = 3 + 3$) to allow testing for significance

Another quantitative measure of the incompetence comparable with the filling time is the *regurgitant volume* which in these patients was determined either by the combined angiographic and dye dilution technique or by continuous dye *infusion and which is expressed in per cent of* the total flow The highest values for the regurgitant fraction were found in the group of patients with a filling time of less than 1 sec the mean value here being 58.2 (40–71)% compared with 31.0 (16–43)% in the group with a filling time of more than 1 sec ($d \sim 27.2\%$, $P < 0.01$).

Included among other haemodynamic and clinical signs used for evaluation of the degree of incompetence were the following *resting pressures,* namely the end-diastolic pressure gradient over the aortic ostium, the directly and indirectly measured diastolic arterial pressure and the total blood pressure amplitude. The direct systemic arterial pressure was measured in the aortic arch at the start of the heart catheterization and not simultaneously with the indirect pressure, which was measured a day or two earlier at the general physical examination. At this blood pressure measurement with the cuff method the tone was *heard down to zero in 11 patients with* $AI_{IV<1s}$ but only in 1 patient with $AI_{IV>1s}$. As is evident from Table 36, the patients of group $AI_{IV<1s}$ with a filling time of less than 1 sec showed a lower diastolic arterial pressure and a lower end-di-

Table 37 *Annular diameter of aortic valve in 61 patients with AI grades I–IV (Mean values)*

AI grade		Annular diameter of aortic valve, mm Systole	Diastole
I		1	1
	Value	32	32
II		5	5
	Mean	37.0	36.2
	Range	28–43	28–43
III		9	9
	Mean	41.1	39.0
	S.D	5.3	6.1
	S.E.M	1.8	2.0
	C.L. 95 %	37.6–44.6	35.0–43.0
IV		46	42
	Mean	40.3	36.1
	S.D	8.9	8.0
	S.E.M.	1.3	1.2
	C.L. 95 %	37.7–42.8	33.7–38.6

astolic pressure gradient over the aortic ostium, and a higher pulse pressure than the patients of group $AI_{IV\ lo}$. The indirectly measured diastolic pressure used for the mean value calculations was that noted on disappearance of the tone from this level the amplitude was determined. It was found that the differences between the groups in question were significant for the diastolic pressure and pulse pressure at the indirect blood pressure measurement, and similarly for the diastolic pressure gradient over the aortic ostium.

Since the end-diastolic volume of the left ventricle (EDV) can influence the entricular diastolic filling time an attempt was made to obtain a measure of the filling rate by calculating the quotient *EDV in ml/filling time in sec*. Here also it was found suitable to divide the patients into two groups: EDV/filling time less than 550 ml/sec, corresponding to $AI_{IV\ lo}$ (13 patients), and greater than or equal to 550 ml/sec, corresponding to $AI_{IV<lo}$ (16 patients). For these calculations the end-diastolic olume was measured from full-size angiograms; the few patients who were examined by cineangiography alone were grouped after conversion of the cineangiographic volumes to corresponding full-size values by means of the correction factor 0.64 which was calculated from the comparison between the two angiographic methods, mentioned previously (see also Table 33). The filling time (mean ±S.E.M.) was 1.22±0.05 sec for the first group and 0.71±0.05 sec for the second group. The two groups were compared with respect to the blood pressure conditions mentioned above, and approximately the same differences were found as in the groups classified according to filling time alone. Thus the mean difference (±S.E.M.) between $AI_{IV<lo}$ and $AI_{IV\ lo}$ for the indirect diastolic pressure was −35.1±10.9 ($P<0.01$) for the indirect and direct pulse pressure 44.7±10.8 ($P<0.001$) and 18.8±8.3 ($P<0.05$) respectively and for the diastolic gradient over the aortic ostium −20.4±6.1 mmHg ($P<0.01$). No significant difference was found between the groups for the directly measured diastolic pressure.

Since the filling time extends over more than one diastole, and the end-systolic olume (ESV) is large the quotient *EDV-ESV in ml/filling time in sec* should constitute a more adequate way of determining the filling rate than through the quotient EDV/filling time alone. In this case also the patients were classified into two groups: EDV ESV/filling time less than 400 ml/sec, corresponding to $AI_{IV\ lo}$ (15 patients) and greater than or equal to 400 ml/sec, corresponding to $AI_{IV<lo}$ (14 patients). In these cases the volumes obtained cineangiographically were converted to corre sponding full-size angiographic volumes by using the correction factor 0.61 (Table 33) The mean filling time (mean ±S.E.M.) for the first group was 1.18±0.05 sec and for the second group 0.69±0.04 sec. Comparison of the blood pressure conditions between the two groups showed mean differences for the indirect and direct arterial pressures of −43.6±9.6 ($P<0.001$) and −11.. ± 3.80 ($P<0.01$) mmHg, respectively for the indirect and direct pulse pressures of 48.1±10.58 ($P<0.001$) and 17.1±8.25 (P approximately 0.05) mmHg, respectively and for the diastolic gradient −21.4±5.70 (P approximately 0.001).

In *AI grade III* the diastolic filling time for the left entricle constitutes the time from the start of the contrast injection to the first exposure in diastole when the entricle is thinly filled with contrast medium. In 7 patients out of 10 with AI of this grade the filling time extended over 2–4 diastoles and in the remaining 3 patients (Nos. 15 17 and 25) who were judged to be cases bordering against AI grade IV over 1.5–..

diastoles. The filling time for complete distribution of the contrast material comprised 2–2.5 diastoles in group $AI_{IV\ ls}$ and 0.5–1.5 in a few cases 2 diastoles, in group $AI_{IV\ ls}$. When the time was expressed in seconds, the following values (mean ±S.E.M. and C.L. 95 %) were obtained for the different groups: 1.23 ± 0.11 (0.98 – 1.48) for AI grade III 1.24 ± 0.05 (1.12 – 1.35) for AI grade IV > 1s and 0.71 ± 0.04 (0.62 – 0.80) for AI grade IV < 1s. The mean difference between $AI_{IV\ ls}$ and AI III was – 0.01 sec, while that between $AI_{IV<ls}$ and AI III was highly significant (– 0.5 ± 0.12 $P < 0.001$). A comparison of the blood pressure values between the 10 patients with AI grade III and group $AI_{IV\ ls}$ also showed only small, non-significant differences, while the differences between AI III and $AI_{IV\ ls}$ were greater and statistically significant for all five parameters (Table 36)

IV *Ascending Aorta, Aortic Valve and Coronary Arteries*

The annular diameter of the aortic valve (Table 37) did not vary greatly between AI grades II III and IV (total). In order to obtain a relative comparative measure the quotient between the annular diameter and the diameter of the descending aorta at the same level was calculated, and it was found that in this case also the differences in question were small and non-significant. The cyclical volume variations in the ascending aorta were most clearly evident in the patients with AI grade IV with their large total stroke volume. The difference in annular diameter between systole and diastole in this group is probably significant. The mean difference (d ± S.E.M.) was 4.1 ± 1.8 mm. The ascending aorta was clearly aneurysmally dilated in altogether 8 patients with AI grade IV. Among 5 of these patients in whom it was possible to measure the annular diameter in systole from full-size angiograms 4 showed a large diameter varying between 56 and 72 mm, but in one case with a bulb-shaped enlargement of the ascending aorta, this annular width was only 36 mm. With regard to the *valve anatomy* a distinct jet of contrast medium through a perforation hole (probably due to bacterial endocarditis) was shown angiographically in one patient (No. 28) and this finding was verified at operation and in another patient an aneurysm of one of the Valsalva sinuses was seen. In just under half of all patients of the series the valves were assessed as thickened—slightly in 30 patients, moderately in 6 patients and greatly in 1 patient. In 19 of these patients the mobility of the valves was slightly reduced and in 11 patients moderately reduced. Of these 37 patients with anatomical changes of the valves, a systolic pressure gradient over the aortic ostium was recorded in a total of 14 patients at a relatively high flow—in 6 cases both at rest and during exercise, and in the remainder only during exercise. The resting gradient varied between 1 and 26 mmHg. Small calcifications, both in the annulus and in the cusps themselves, were observed on the angiographic films in 15 patients, in most of whom the aetiology was rheumatic in a few cases the aetiology was unknown.

A rough assessment of the *coronary arteries* was possible in 70 patients from films obtained at thoracic aortography and angiography of the left atrium or ventricle. In about half of these patients the coronary arteries could only be assessed partly however. In no patient was selective coronary angiography performed. A total of 4 patients (Nos. 24 25 65 and 109) in two of whom (Nos. 65 and 109) the aortic incompetence had a *syphilitic* background, *arteriosclerotic changes* in the coronary arteries were observed but in two of them (Nos. 65 and 109) these consisted in only slight irregularities of the vessel wall. Examination of the two other patients (Nos. 24 and 65) who had a history of severe angina pectoris, revealed constrictions down to half of the normal width but with no appreciable reduction of the flow rate as determined angiographically

V *Mitral Incompetence*

Mitral incompetence was demonstrated angiocardiographically in 5 of the 81 patients of this series (Nos. 70 84 88 89 and 106). Since all of these patients had aortic incompetence of grade IV with rapid and complete filling of the left ventricle on injection of contrast medium into the ascending aorta, the regurgitation to the left atrium could be evaluated at the thoracic aortography without any interference from arrhythmias. In 4 patients the mitral incompetence was assessed as mild and in 1 patient (No. 84) as

Table 38. *Frequency of arrhythmia during angiocardiography*

Angiocardiography Site of injection	Total No. of investigations	Ectopic beats Supraventricular single beats 1	 2	 3–4	Ventricular single beats 1	 2	 3 or more in series
Left atrium	59	14	7	4	6		
Left ventricle	26				6		16
Ascending aorta	109				7		

moderate in the latter patient thin filling of the atrium was obtained both at thoracic aortography and retrograde left ventricular angiography (the cine method)—the latter examination was more difficult to evaluate, however due to ventricular tachycardia (150 beats/min) with 17 ventricular extrasystoles in series immediately after the end of the injection. In one other of these patients cineangiography was performed from the left ventricle, but this time through the transseptal catheter since an attempt at reaching the left ventricle retrogradely was unsuccessful, during the contrast injection a series of six ventricular ectopic beats with a frequency of 140 beats/min was induced, which considerably complicated the evaluation of the degree of incompetence which at this examination was assessed as rather more pronounced than on contrast injection into the ascending aorta. In a further 18 patients a protracted apical systolic murmur mostly of a strength of 3–4/6, had led to the retrograde left ventricular angiographic examination (in cases full-size angiography and in 16 cases cineangiography). In none of these patients was any definite leakage of contrast material to the left atrium observed. In 8 patients, however the evaluation was uncertain owing to a large number of ventricular extrasystoles (3 or more in series) during the injection but in these cases no mitral incompetence was revealed by the thoracic aortography

VI. *Complications during the Angiographies*

Intramural contrast injection with leakage of a small amount of contrast material into the pericardial sac occurred in one patient (No 20) during retrograde left ventricular angiography 7 ventricular ectopic beats were noted during the injection and 9 during further exposures. No special measures were required. During the contrast injection the patient had moderate pain in the chest, which gradually disappeared within the next 12 hours. No fall in blood pressure occurred and neither were there any initial ECG changes as in a fresh myocardial lesion. No elevation of serum glutamic oxalacetic transaminase (SGOT) followed. After one week the investigation could be complemented with further left ventricular angiography and thoracic aortography and no complications occurred during these examinations.

Arrhythmias occurred frequently during the left atrial and left ventricular angiographies (in 53 and 85% respectively) as can be seen in Table 38. During the thoracic aortographies there were no cases of asystole but in 7 patients occasional ventricular extrasystoles occurred, which in 4 patients were probably induced by the transseptal catheter which was placed in the left ventricle for pressure measurement during the angiography in order to allow at the same time a construction of pressure-volume curves. In a few patients the arrhythmia could be explained by the fact that during diastole after completion of the injection the retrograde catheter slipped down into the left ventricle. The supraventricular arrhythmia associated with the contrast injection into the left atrium and the single ventricular ectopic beats which were noted at the different forms of angiography may be regarded as not dangerous from the arrhythmia point of view To be looked upon as potentially hazardous, however are the short or long attacks of ventricular tachycardia during the left ventricular injections with 3–9 ventricular ectopic beats in sequence in 19 cases and 13–29 ventricular ectopic beats in sequence in 5 cases, even though they all started in association with the injection period, ceased spontaneously and in these cases led to no sequelae. During these periods of more severe arrhythmia with ventricular tachycardia, not only was an increase in heart rate up to 120–130 beats/min observed but in two patients also a considerable, transient blood pressure reduction to 80/65 and 75/55 mmHg, respectively Only 3 retrograde left ventricular angiographic examinations were free of arrhythmia, and in of these patients the catheter recoiled to the ascending aorta during the contrast injection.

DISCUSSION

Left ventricular volumes

The methods of angiocardiographic examination used for calculation of the end-diastolic (EDV) and end-systolic volumes (ESV) of the left ventricle and of the stroke volume (SV) and ejection fraction (SV_t/EDV) have been found, together with haemodynamic studies, to be of value for assessment of the left ventricular function and for obtaining an idea of the relative importance of any associated myocardial disease in patients with valvular disorders. Angiographic measurement of the left ventricular volumes has also proved of value for calculation of the regurgitant volume in valvular incompetence. With the introduction of the cineangiographic method, with its rapid exposure frequency better possibilities have been obtained for estimating the left ventricular volumes and studying the cardiac function by means of analysis of volume curves and pressure volume curves.

Another technique which has come into use in many places for determination of the volumes of different chambers of the heart is indicator dilution. Dye dilution was introduced by Swan and Beck (1960) for measurement of left ventricular volumes by continuous recording of densitometer curves. This technique has since been used by Levinson et al (1967) and Wilcken (1968) while Hugenholtz et al. (1968) has employed the fiber optic method. The radioisotope indicator technique with external scanning, was introduced in 1962 by Folse and Braunwald. Rapaport and coworkers (1961) were the first to use thermodilution for determination of left ventricular volumes.

Values for left ventricular volumes obtained by means of angiocardiography and by indicator dilution techniques (dye dilution and thermodilution) have been given by several authors for patients both with and without heart disease. Table 39 summarizes the results which have been arrived at by different investigators. The angiographic methods included in the table are those which are most commonly used, and have been reported by Arvidsson (1961) and Dodge et al (1960). The designation "normal" in the table refers to patients with no signs of heart disease. There is some doubt as to whether the values for Arvidsson's group of patients with different cardiac lesions without incompetence really can be considered to represent left ventricular volumes in normal persons, but they would seem to be of some interest from a comparative aspect, since our left ventricular volumes were calculated by this method. Comparison with Arvidsson's values is also rendered difficult by the fact that he carried out his angiographic examinations under general anaesthesia and positive intrathoracic pressure, which may explain the finding that his values are relatively low compared with those obtained by other authors using the same method. Values for left ventricular volumes in different types of valve disease have been reported by Jones et al. (1964), Hermann and Bartle (1968), Dodge and Baxley (1969) and Chatterjee et al. (1971) among others, and by Dodge et al. (1966) in a series of patients with myocardial disease. Apart from the normal values, Table 39 only refers to patients with aortic incompetence.

The end-diastolic volumes obtained angiographically are usually regularly larger than those found in model studies in humans (Dodge et al. 1960, Greene et al. 1967, Rackley et al. 1967 and Bruns 1970) as well as in dogs (Chapman et al. 1958, Gribbe et al. 1959, Sanmarco and Bartle 1966). This is probably due partly to the inclusion of papillary muscles, trabeculae carneae and chordae tendineae in the living heart and the effect of a sudden injection of a large amount of contrast material. It must be taken into account that the injected contrast medium may influence the left ventricular function both mechanically by the rapid administration of a relatively large volume of fluid, and through the hyperosmotic properties of the contrast material.

The mechanical effect, which has been studied by Hallermann et al. (1964) and Carleton and Clarke (1969) in animal experiments, seemed to be of lesser importance in our investigations. Thus, in a comparison in 18 of our patients, between the arterial blood pressure measured before the contrast injection and during the actual angiography at the time point for the volume measurements, no significant difference was found either for the systolic or diastolic arterial pressure nor for the heart rate, which was noted in 47 patients both before and during the full-size angiographies. The mean difference ($\bar{d} \pm$ S.E.M.) for the systolic arterial pressure was -2.1 ± 2.3 mmHg, for the diastolic arterial pressure $-0.11 \pm$

Table 39 *Left ventricular volumes in adults. (A) normal subjects and (B) patients with aortic incompetence*

Data collected from the literature. Mean values are given, followed in brackets by S.D. The values of Hermann and Bartle (1968) and Levinson et al. (1971) have been recalculated to S.D. Values in parentheses are ranges.
EDV = end-diastolic volume, ESV = end-systolic volume.

Author	Method	Diagnosis	Pat. No.	EDV (ml)	EDV (ml/m²)	ESV (ml)	ESV (ml/m²)	Ejection fraction
A								
I. *Angiocardiographic methods*								
Arvidsson 1961	Arvidsson	Without valvular incompetence	16		57.2 [18.2]		14.7 [7.3]	0.74
Björk and Lodin 1965	Arvidsson	Normal	4	152 (125–183)		21 (17–33)		
Arvidsson 1966	Arvidsson	Normal	11		72		20	
Hermann and Bartle 1968	Arvidsson	Normal	6		103 [20]		47 [13]	0.54 [0.09]
Dodge and Tannenbaum 1956	Dodge	Normal	11		60–131			
Hay et al. 1961	Dodge	Without left heart disease	20		90 [18]			
Sandler et al. 1963	Dodge	Normal	23		100 [25]			
Kennedy et al. 1966	Dodge	Normal	16	125 [31]	70 [20]	42 [17]	24 [10]	0.67 [0.08]
Hermann and Bartle 1968	Dodge	Normal	6		71 [18]		30 [9]	0.58 [0.04]
Yaguramu and Wakabayashi 1969	Dodge	Normal	4	108 (94–117)		36 (22–44)		0.67 (0.57–0.79)
Tyrell et al. 1970	Dodge	Normal	—		(50–80)			(0.60–0.75)
Chatterjee et al. 1971	Dodge	Normal	7		70 [17]		21 [7]	0.70 [0.03]
II. *Indicator dilution methods*								
Levinson et al. 1967	Dye dilution	Normal	11		82 [12]		37 [11]	0.55 [0.08]
Wicken 1968	Dye dilution	Normal	9		95 [7.5]			0.52 [0.05]
Krayenbühl et al. 1969	Thermodilution	Normal	11		107 [28]			0.50 [0.06]
B								
I. *Angiocardiographic methods*								
Miller et al. 1965	Arvidsson	AI	10		264 (110–448)		152 (35–290)	0.44 (0.34–0.68)
Hermann and Bartle 1968	Arvidsson	AI	7		217 [58]		96 [54]	0.57 [0.15]
Jones et al. 1964	Dodge	Aortic valve disease						
		Regurg. flow 0–20 ml 15 [8]	9	181 [58]	98	99 [61]	54	
		21–50 ml 33 [9]	8	215 [48]	121	108 [57]	61	
		> 50 ml 58 [12] %	17	293 [89]	161	126 [64]	69	
Kennedy et al. 1968	Dodge	AI	38		197 [64]		89 [36]	0.55 [0.10]
Hermann and Bartle 1968	Dodge	AI	7		174 [64]		76 [34]	0.58 [0.07]
Dodge and Baxley 1969	Dodge	AI Regurg. flow 30 ml/beat	22		193 [55.4]			0.56 [0.13]
Tyrell et al. 1970	Dodge	AI	27		151 (70–422)			(0.43–0.85)

Table 39 (*continued*)

Author	Method	Diagnosis	Pat. No.	EDV (ml)	EDV (ml/m²)	ESV (ml)	ESV (ml/m²)	Ejection fraction
II. *Indicator dilution methods*								
Hugenholtz et al. 1968	Fiberoptic dye dilution	AI	7		(85.7–166.0)			
Wilcken 1968	Dye dilution	AI	4		201 (166–202)			
Bristow et al. 1964	Thermodilution	AI	7		218			
Bristow et al. 1966	Thermodilution	AI	13		201 (108–373)			
Krayenbühl et al. 1969	Thermodilution	AI	16		216 [77]			0.43 [0.16]
Lewis et al. 1971	Thermodilution	AI	21		234 [81]			

1.9 mmHg and for the heart rate 2.3 ± 1.6 beats/min

The hyperosmotic properties of the contrast medium, however, have more prolonged and marked pharmacodynamic and haemodynamic effects. These are manifested in the form of a reduction of the systemic arterial pressure with an accompanying increase in the heart rate 10–15 sec after completion of the injection and 1–2 min later a large increase in the cardiac output due partly to peripheral vascular dilatation with *an increased peripheral blood flow* caused by the contrast medium (Delius and Erikson 1969, Lindgren 1970, Coel and Lasser 1971) and partly to a transient plasma volume increase with a clearly visible fall in haematocrit, which in turn is partly due to shrinkage of red blood cells (Brown et al. 1965, Friesinger et al. 1965, Iseri et al. 1965, Björk 1966, Rahimtoola et al. 1966, Bristow et al. 1967, McIntosh et al. 1967). The hypotension is probably due to a combination of a direct negative inotropic effect of the contrast agent on myocardial contraction (Björk 1971) and a direct peripheral arteriolar dilatation (Zelis et al. 1970). The increased volume of circulating blood leads to a transient increase in intracardiac pressure and increased stroke work (Brown et al. 1965, Rahimtoola et al. 1966 and 1967). After coronary arteriography in normal subjects and in patients with varying degrees of coronary arterial disease Gensini et al. (1971) observed that the greatest increase in left ventricular end-diastolic pressure occurred in those patients with the most severe left ventricular myocardial disease. In a study of 23 patients with aortic incompetence Brown et al. (1969) found that only half of the patients showed a rise in the end-diastolic pressure to above 12 mmHg after angiography and that there was no correlation between the degree of severity of the regurgitation and the end-diastolic pressure of the left ventricle after angiography.

Carleton and Clark (1969) in their animal study referred to previously observed both an increase in size of the left ventricle immediately after injection of saline and reduced myocardial contractility for a few seconds after the injection of the hyperosmotic contrast medium, regardless of whether the injection was given into the left ventricle or the aorta. Increased left ventricular dimensions were also found by Sanmarco et al. (1966) while Levinson et al. (1966) showed a dose-related initial decrease of the left ventricular volumes. The haemodynamic changes, which may be attributed to the hyperosmotic properties of the contrast medium, would seem to occur mainly after completion of the injection and thus will not affect the volume measurements (Miller and Swan 1964). Between the time points for the mechanical and pharmacodynamic effects on the circulation there will thus be a free interval, in which the calculations may be assumed to be relatively true. Carleton (1971) analysed 5 consecutive cardiac cycles from left ventricular angiograms in 7 patients and he observed a small progressive increase in left ventricular volumes from the third opacified cardiac cycle. Normalization of the pressure and blood values usually takes place within 15–20 min after the end of the injection. For this reason, when several angiographies are performed in series we wait

for a return of the arterial blood pressure and heart rate to approximately the initial level before conducting a further examination which in general means an interval of 20–30 min between the examinations. The pressure changes are easily noted and may be assumed to run parallel with the other haemodynamic reactions (Carleton and Clark 1969)

Technical difficulties in the measurements affect mainly the determination of the end-systolic volume since the ventricular contour which is formed here by the inner surface of the trabeculae carneae, often is irregular and deviates from the ellipsoidal form. The uncertainty is particularly great in cases of small volumes. There is a tendency towards underestimation of ESV and consequently an overestimation of SV_t, but for the determination of SV a percentage error in the calculation of ESV is of relatively less importance than an error in the calculation of EDV In patients with great enlargement of the left ventricle, for example in aortic incompetence, the risk of an erroneous evaluation of the volumes is smaller and therefore in these cases the angiographic method can be considered more acceptable. According to Arvidsson (1961) the errors caused by the trabecular network can be compensated for by including only half of its thickness in the volume calculation we have used this mode of procedure

Hermann and Bartle (1968) made a comparative study of left ventricular volumes calculated from biplane angiograms by the method of Arvidsson and by the area length method of Dodge. As is evident from Table 39 they found that in normal cases Arvidsson's method gave 35% higher values for EDV and 30% higher values for ESV while the percentage difference in the patients with aortic incompetence, with their larger volumes, was smaller—about 20% for both end-systole and end-diastole. The difference between the methods can be explained by the fact that in the area length method an equation is used which compensates for papillary muscles and trabeculae and that the transverse diameters for both antero-posterior and lateral projections are significantly smaller in planimetric calculations than with direct measurement.

These results have been verified by Hawley et al. (1965) and by Hugenholtz et al. (1968) In comparative studies, these latter authors found an average overestimation of 22% in volume calculations by the Arvidsson method. Dodge et al. (1966) showed a linear correlation ($r = +0.975$) between the volumes calculated by these two methods, as also did Hugenholtz et al. (1968) who obtained a correlation coefficient of +0.984 for EDV +0.957 for ESV and +0.984 for SV We have made similar findings in comparisons between EDV and ESV calculated from biplane full-size angiograms according to the method of Arvidsson and from single plane cineangiograms; we found the correlation coefficients to be +0.98 and +0.996 respectively (Fig. 36) which is in good agreement with the relationship reported by Greene et al. (1967) between single plane cine angiographic volumes and biplane large film volumes measured by a slight modification of the Arvidsson method ($r = +0.988$ for EDV+ESV). They found the greatest difference between the methods in cases with an ESV greater than 200 ml, when the cineangiographic volume was as little as 50% of the biplane volume. As has already been mentioned under "Results" a systematic difference was also found in the present study—the values obtained by the cineangiographic method were, on the average only about 2/3 of those obtained by the Arvidsson method, with the smallest scatter for EDV (S.D 8.2%) as can be seen in Table 33

In comparisons between left ventricular volumes determined by angiocardiography (Dodge's method) and the indicator dilution technique, most investigators have found higher values for EDV and ESV with the latter method (Sanmarco and Bartle 1964 Bartle and Sanmarco 1966 *a*, Sanmarco et al 1966 Hugenholtz et al. 1968, among others) which is considered to be due to unsatisfactory left ventricular mixing (Swan and Beck 1960 Irisawa et al. 1960 Swan et al. 1965). On the other hand, Rapaport and co-workers (1961) in their estimations of left ventricular volumes by means of thermodilution obtained good reproducibility which they interpreted as a sign of relatively complete ventricular mixing. Further Frank et al. in a recent article (1971) describing the results of a comparison between left ventricular volumes determined by single-plane cineangiography and the dye dilution technique reported good agreement between the methods ($r = +0.98$) with no significant mean differences either for EDV ESV or SV

of AI. 69% of the patients with AI grades III and IV had *pulsus celer et magnus* and 72% had a femoral arterial sound. Relatively good agreement was found between the pulse phenomena and the directly and indirectly measured pulse pressures. The indirectly measured systolic popliteo-brachial gradient increased successively with increasing grade of incompetence from an average of 25 mmHg in AI grades I and II to 58 mmHg in AI_{IV} ... This indirectly measured gradient is exaggerated and considerably higher than that measured directly but it facilitates differentiation of the severity of the regurgitation. On indirect blood pressure measurement a successive increase of the systolic pressure and blood pressure amplitude and a successive decrease of the diastolic pressure were obtained for the latter the same was true on direct measurement of the central aortic pressure. On indirect measurement of the diastolic pressure it was found that the level of muffling of the sounds gave the most reliable values; these mean values lay 1–6 mmHg higher than those obtained on direct intraarterial measurement.

All patients in this series except two had sinus rhythm. The exception was a 59-year-old man with atrial fibrillation and a 62 year-old man with an implanted fixed-rate pacemaker. Sixteen patients had a prolonged A V conduction time of these 15 were receiving digitalis. With increasing grade of incompetence the QRS amplitude increased successively. Patients whose ECG showed a typical pattern of left ventricular hypertrophy were found to have significantly larger end-diastolic volumes and thicker left ventricular walls than patients with a normal or borderline-normal ECG.

During the physical work test 11 patients showed an elevation of the T wave from negative or flat at rest to positive during exercise. In 4 patients with a normal ST–T segment in ECG at rest (who were not having digitalis) an ST–T pattern as in left ventricular hypertrophy was provoked during exercise.

A typical picture of the changes that may take place in the clinical course in progressive aortic incompetence is seen in Table 40 which refers to a male 54-year-old patient (No 42) who had a dilated ascending aorta due to medionecrosis cystica.

At an early well compensated stage of the valvular disease fairly normal intracardiac pressure values and flow values are found. A slight systolic pressure gradient over the aortic ostium was recorded in 18 patients at rest and 28 patients during exercise. At rest, this amounted to an average of 8 (1–26) mmHg and during exercise to 13 (1–35) mmHg. However only once did the value at rest exceed 20 mmHg, and four times during exercise. These patients had free, pronounced AI of grade IV. In none of the cases with a systolic pressure gradient over the aortic ostium were there any definite signs of true anatomical stenosis.

It was of especial interest to note that the diastolic aortic pressure was, on the average as high as about 60 mmHg in AI grade IV with maximal values up to about 85 mmHg, even in a non-decompensated stage.

In patients whose AI was in an early well compensated stage the left ventricular filling pressure decreased and the effective stroke volume increased during exercise in the supine position. The same finding was made in patients with severe AI as long as their functional capacity was good. The majority of these patients were below 45 years of age. In patients with a history of left ventricular failure the effective flow at rest was generally lower than the corresponding normal value. These patients had a low average value of the exercise factor"—368—as against 660 in AI grades I and II. In some cases with severe AI there was a decrease in the effective stroke volume during exercise and a simultaneous increase in the left ventricular filling pressure, which was already elevated at rest. During muscular exercise in the supine position a decrease in the regurgitation was observed there was an intimate relationship between this reduction of the regurgitant fraction and the increase in heart rate.

On inhalation of amyl nitrite which causes peripheral vasodilatation and a decrease in the total peripheral resistance with an ensuing blood pressure reduction and secondary to this an increase in the heart rate and cardiac output, a mode of reaction similar to that in muscular work is induced. A study was made in some patients of the effect of amyl nitrite on the diastolic regurgitant murmur and on certain central haemodynamic factors. At the height of its effect the left ventricular end-diastolic pressure decreased markedly the effective forward flow increased

greatly and there was also an increase, but to a lesser extent, in the stroke volume together with these effects the diastolic murmur diminished, and in some cases disappeared entirely

As it was found that the stroke volumes deter mined angiocardiographically (from full-size angiograms according to the method of Arvidsson or from cineangiograms) were higher than the cor responding values obtained by the Fick method or the dye dilution technique all angiocardiographically measured stroke volumes were cor rected by empirically obtained factors, one for each method, before calculation of the regurgitant volume by the combined angiographic and dye dilution technique. For conversion of the full-size angiographic value to the corresponding Fick value the correction factor 0.42 was obtained and used for the cineangiographic stroke volumes the factor was 0 70 On direct comparison between full-size angiography and cineangiography a systematic difference was found between the methods, with considerably higher val es for the volumes calculated by the former method Thus the end-diastolic volume measured cineangiographically was, on the average 64% of that calculated from full-size angiography and the corresponding value for both the end-systolic volume and the left ventricular stroke volume was 61% There was, however a good correlation between the two methods for the end-systolic ($r = +0.996$) and end-diastolic volumes ($= +0.98$). A progressive increase in the left ven tricular volumes was found with increasing degree of AI. The volume increase in AI grades III and IV was considerable. There was a clear relationship between the left ventricular end-diastolic volume and the regurgitant volume, expressed as per cent of the total flow The coefficient of cor relation between t regurgitant fraction deter mined by the co tinuous dye infusion method and the end-diastolic volume measured by full-size angiography was $= +0.81$ and by cineangiography $= +0.76$.

On comparison between different AI grades (determined by thoracic aortography) and the magnitude of the regurgitant fraction (determined by the continuous dye infusion method) a marked variation was found in the regurgitant fraction, from a minimum of 33% to 76% in AI grade IV In patients with AI grade II the regurgitant fraction was lower than 30% and the same was found for AI grade III with one exception. Between the two groups of patients with a regurgitant fraction of below and above 30% there was a significant difference in the indirectly measured diastolic pressure and pulse pressure. In 30 patients with AI grade IV and 10 patients with grade III it was possible to calculate the total diastolic filling time for the left ventricle. The patients with AI grade IV were classified into two sub-groups according to the magnitude of the filling time: AI_{IV} [illegible] (13 patients) and AI_{IV} [illegible] (17 patients). The mean regurgitant fraction was 58% in group AI_{IV} [illegible] and 31% in group AI_{IV} [illegible]. There were significant differences between the groups for the indirectly measured diastolic pressure and pulse pressure and for the end-diastolic pressure gradient over the aortic ostium. Even though a direct comparison between the filling times for AI grade III and AI grade IV > 1s is limited by methodological factors, it seems justifiable to conclude that patients of group IV > 1 differ more from group IV < 1s than from AI grade III as regards the severity of the incompe tence as assessed from the blood pressure measurements.

The patients with AI grade IV combined with MI did not differ with certainty from th patients with isolated AI_{IV} as regards total heart olume and left entricular olumes, but there was a difference in the intracardiac pressures Two of these 5 patients showed noteworthy pressure reaction during exercise in the form of a reduc tion of the pressure in the left atrium, which might ha been secondary to reduction of the aortic regurgitation.

APPENDIX 2. STATISTICAL METHODS

Conventional statistical methods were used (Fisher 1930, Hoel 1966).

The *error of the method* based on duplicate determinations, was calculated according to the formula (Enghoff 1937): $\sqrt{\sum d^2/2n}$, where d is the observed difference between the two determinations and n is the number of duplicate determinations.

The *residual standard deviation* (S.D.) from the regression line was calculated according to the formula

$$\sqrt{\frac{n}{n-2}(1-r^2)\left(\frac{\sum y^2}{n}-\bar{y}^2\right)}$$

Since the conventional formula for calculation of the *mean error* of the correlation coefficient only has very limited validity Fisher's z-transformation was used for the computation of confidence limits (C.L.) for the true coefficient of correlation (cf. Hoel 1966): the 95% confidence limit values obtained were then transformed to apply to r.

Significance levels. The term "significant" is used in accordance with the following convention. If an observed mean difference or the difference between two means is of such magnitude that the probability (P) of obtaining a difference at least as high as the observed value is greater than 0.05 (where the null hypothesis is assumed to hold), then that observed difference is said to be non-significant.

If $0.01 < P \leq 0.05$ the difference is said to be probably significant.

If $0.001 < P \leq 0.01$ the difference is said to be significant.

If $0.001 \geq P$ the difference is said to be highly significant.

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REFERENCES

Adams, C. W Aortic insufficiency "Original" descriptions. Amer J Cardiol. 4 731 1969

Akar, U T Friedenberg, M. J & Parker B. M., Retrograde left ventricular angiocardiography and aortography Circulation 29 34 1964

Aldridge, H. E., The estimation of aortic insufficiency Canad. med. Ass. J 87 941 196..

Amplatz, K., Lester R. G., Ernst, R. & Lillehei, C. W Left retrograde cardioangiography: its diagnostic value in acquired and congenital heart disease. Radiology 76: 393, 1961.

Areskog, N. H. & Hallén, A., ECG at rest and ECG response to exercise. Acta chir scand. Suppl. 323 70, 1964

Armelin, E., Donald, D E. & Wood, E. H. Comparison of dilution technics using aortic injection with upstream sampling for assessment of aortic regurgitation. Circulat Res. 15 287 1964

Armelin, E., Michaels, L., Marshall, H. W Donald, D E., Cheesman, R. J & Wood, E. H., Detection and measurement of experimentally produced aortic regurgitation by means of indicator-dilution curves recorded from the left ventricle. Circulat. Res. 12: 269 1963

Arvidsson, H Angiocardiographic observations in mitral disease with special reference to volume variations in the left atrium. Acta radiol. Suppl. 158 1958.

Arvidsson, H Angiocardiographic determinations of left ventricular volume Acta radiol. 56: 321 1961

Arvidsson, H Angiocardiographic measurements in congenital heart disease III. Size of left ventricle including analysis of normal ventricular volume in systole and diastole Acta radiol 4 155 1966

Arvidsson, H & Karnell, J Quantitative assessment of mitral and aortic insufficiency by angiocardiography Acta radiol. 105 1964

Astrand, Irma The physical work capacity of workers 50–64 years old Acta physiol scand 42 73 1958

Astrand, Irma Aerobic work capacity in men and women with special reference to age Acta physiol. scand Suppl 169 1960

Astrand, P.-O Experimental studies of physical working capacity in relation to sex and age Ejnar Munksgaard, Copenhagen 195

Bäcklund, L Bergstrom, K Ericsson, P Eriksson, U Hootfeldt, B A Ranck, H Val av mat arabler för att predikta hjärtvolym T be published

Baggenstoss, A. H & Rosenberg, E F Cardiac lesions associated with chronic infectious arthritis Arch Intern. Med. 67 241 1941

Babcock, H. T & Nelson A R C ic medial necrosis as cause of localized aortic ne ms amenable to surgical treatment. Ann Surg 144 9 19 6

Bailey C. P & Zimmerman, J Aortic regurgitation. Handbuch der Thoraxchirurgie, Bd. 2. Springer Verlag. Berlin-Göttingen-Heidelberg. 1959

Barlow J & Shillingford, J The use of amyl nitrite in differentiating mitral and aortic systolic murmurs. Brit. Heart J 20 162, 1958

Barondess, J A. & Sande, M.: Some changing aspects of aortic regurgitation. Arch. Intern. Med. 1 4 600, 1969

Barrett, J S., Helwig, J J Kay C. F & Johnson, J.s Cine-aortographic evaluation of aortic insufficiency Ann. Intern. Med. 61 1071 1964

Bartle, S. H. & Sanmarco, M. E.: Measurement of left ventricular volume by biplane angiocardiography and indicator-washout technique: a comparison in the canine heart. Circulat. Res. 19 295 1966 a.

Bartle, S H. & Sanmarco, M. E., Comparison of angiocardiographic and thermal washout technics for left ventricular volume measurement. Amer. J Cardiol. 18. 235 1966 b

Baxley W A., Dodge, H. T & Sandler, H., A quantitative angiocardiographic study of left ventricular hypertrophy and the electrocardiogram. Circulation 37 509 1968

Beck, W Schrire, V Vogelpoel, L., Nellen, M. & Swanepoel, A., Hemodynamic effects of amylnitrite and phenylephrine on the normal human circulation and their relation to changes in cardiac murmurs. Amer. J Cardiol. 8 341, 1961.

Beck, W Schrire, V & Vogelpoel, L., The hemodynamic effects of amyl nitrite and phenylephrine in patients with mitral stenosis and severe pulmonary hypertension. Amer Heart J 64 631 1962.

Bedford, P D & Caird, F L. Valvular disease of the heart in old age. J and A. Churchill Ltd., London 1960

Beerman, H., Nicholas, L., Schamberg, I. L. & Greenberg, M. S. Syphilis. Review of the recent literature, 1960–1961 Arch. intern. Med. 109 323, 1962.

van Bergen, F H., Weatherhead, D S., Treloar, A. E., Dobkin, A. B. & Buckley J J Comparison of indirect and direct methods of measuring arterial blood pressure Circulation 10: 481, 1954

Berglund, E., Birath, G., Bjure, J Grimby G Kjellmer, I., Sandqvist, L. & Söderholm, B., Spirometric studies in normal subjects. I. Forced expirograms in subjects between 7 and 70 years of age Acta med. scand. 173 185 1963

Berglund, E & Söderholm, B., Kompendium i lungsjukdomarnas kliniska fysiologi. Svenska nationalföreningen mot hjärt och lungsjukdomar AB Göteborgs fototryck 1963.

Bergström, K. Röntgenologisk hjärtvolymsbestämning.

Acta Univers. Upsal. Abstracts of Uppsala Dissertations in Medicine, 64 1949

Bergström, K., Bäcklund, L., Erikson, U & Gustafsson, B. Heart volume and its relation to measures of circulatory function in healthy young men. Acta med. scand. 185 471, 1969 b

Bergström, K. & Erikson, U Röntgenologisk hjärtvolymsbestämning. En enkätundersökning. Läk. Tidn. 68 2599 1971.

Bergström, K., Erikson, U & Gustafsson, B., Roentgenological determination of the heart volume. Acta Soc. Med. upsalien 74 81, 1969 a.

Bernmeier A. Die koronare Blutversorgung bei den Klappeninsuffizienzen des linken Herzens. Verh. dtsch. Ges. Kreisl.-Forsch. 31 51, 1965

Bernstein, L. & Brock, O. J., Cardiac complications in spondylarthritis ankylopoietica. Acta med. scand. 135 185, 1949

Bernstein, L., D'Silva, J L. & Mendel, D., The effect of the rate of breathing on the maximum breathing capacity determined with new spirometer. Thorax 7 255 1952.

Beuren, A. J Angeborene Herzklappeninsuffizienz. Verh. dtsch. Ges. Kreisl.-Forsch. 31. 60, 1965

Beuren, A. J & Apitz, J Selektive transseptale Angiokardiographie des linken Vorhofes oder linken Ventrikels. Z. Kreisl.-Forsch. 51 20, 1962.

Beuren, A. J & Apitz, J Left ventricular angiocardiography by transseptal puncture of the left atrium. Circulation 28 209 1963

Bevegård, S., Carlens, E., Jonsson, B & Karlöf, I A technique for transseptal left heart catheterization via the right external jugular vein. Thorax 15 299 1960.

Bevegård, S Jonsson, B. & Karlöf, L. Percutaneous technique for transseptal left heart catheterization via the right femoral vein. Scand. J clin. Lab. Invest 13 439 1961

Bevegård, S., Jonsson, B. & Karlöf, L. A modified instrument for percutaneous transseptal catheterization of the left atrium Scand J clin. Lab. Invest. 15 436, 1963.

Birath, G Crafoord, C. & Rudström, P Pulmonary function after pneumonectomy and lobectomy J thorac. Surg. 16. 492, 1947

Birath, G., Kjellmer I & Sandqvist, L. Spirometric studies in normal subjects II. Ventilatory capacity tests in adults. Acta med scand. 173 193, 1963.

Bishop, J M & Wade, O L Relationships between cardiac output and rhythm, pulmonary vascular pressures and disability in mitral stenosis Clin. Sci. 24 391 1963.

Bos, K. Stokes-Adams disease of undetermined etiology A new hemodynamic concept. Cor et Vasa (Praha) 7 (2) 85, 1965

Björk, L. The osmotic effects of urografin 76 per cent and hypaque 60 per cent in angiocardiography Amer J Roentgenol. 98 922, 1966.

Björk, L. Semi-automatic construction and computer analysis of volume curves and pressure-volume curves in left ventricular cineangiography Acta radiol. 10 413, 1970.

Björk, L. Studies on the acute effects of clinical angiocardiography on left ventricular function. Fortsch. Röntgenstr 115 517 1971.

Björk L. & Callhed, L. Coronary arteriography in valvular heart disease. Acta med. scand. 185 531 1969

Bjork, L. & Lodin, H. Angiographic determination of left atrial and left ventricular volumes in normal children and adults. Acta radiol. 3 577 1965

Björk, V O Callhed, L & Lodin, H Aortic stenosis. Correlations between pressure gradient and left ventricular angiocardiography Circulation 23 509 1961.

Bjork, V O. & Lodin, H. Left heart catheterization with selective left atrial and ventricular angiocardiography in the diagnosis of mitral and aortic valvular disease. Progr cardiovasc. Dis. 116, 1959

Bjure, A. & Laurell, H. Om abnorma statiska cirkulationsfenomen och därmed sammanhängande sjukliga symptom. Den arteriella orthostatiska anämin en försummad sjukdomsbild Upsala Läk.-Fören. Forh. 33 1 1927/28.

Bland, E. F & Wheeler E. O. Severe aortic regurgitation in young people. New Engl. J Med. 256. 667 1957

Blasck, A., Lewis, J & Marcus, F L. Aortic regurgitation in the elderly Amer Heart J 71. 627 1966

Bloomfield, D A., Battersby E. J & Sinclair Smith, B. C. Use of indicator dilution techniques in measuring combined aortic and mitral insufficiency Circulat. Res. 18 97 1966.

Blount, S G Bacterial endocarditis. Amer. J Med. 38 909 1965

Boden, E. & Bayer O. Die Bedeutung des mittleren Aortendruckes für die Koronardurchblutung bei Aortenisuffizienz und Aortenisthmusstenose. Verh. dtsch Ges. Kreisl.-Forsch. 15 225, 1949

Boden, E. & Bayer O Formveränderungen des Ekg bei Aorteninsuffizienz in Abhängigkeit von Blutdruck und Herzfrequenz. Arch. Kreisl.-Forsch. 16 1, 1950

Bordley J Connor, C. A. R., Hamilton, W F Kerr, W J & Wiggers, C. J Recommendations for human blood pressure determinations by sphygmomanometers. Circulation 4 503, 1951.

Bousvaros, G A. & Lenoff, M H. Inhalation of amyl nitrite useful test in the assessment of heart murmurs. Guy Hosp Rep. 111 1 196..

Braun, J The significance of the electrocardiographic pattern for assessment of the degree and type of left ventricular hypertrophy Cardiologia 46. 3, 1965

Braunwald, E., Brockenbrough, E. C., Frahm, C. J & Ross, J., J Left atrial and left ventricular pressures in subjects without cardiovascular disease. Circulation 24 267 1961

Braunwald E., Brockenbrough, E. C., Talbert, J L Folse, J R & Rockoff, S D Selective left heart angiocardiography by the transseptal route Amer J Med. 33 213 196..

Braunwald, E., Fishman, A. P & Cournand, A. Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. Circulat. Res. 4 100, 1956.

Braunwald, E. & Morrow A. G. A method for the detection and estimation of aortic regurgitant flow in man. Circulation 17: 505, 1958.

Braunwald, E. & Ross, J. Jr. The ventricular end-diastolic pressure. Amer. J. Med. 34: 147 1963.

Braunwald, E. & Swan, H. J. C. Cooperative study on cardiac catheterization. Circulation 37 Suppl. 3, 1968.

Brawley R. K. & Morrow A. G. Direct determinations of aortic blood flow in patients with aortic regurgitation. Effects of alterations in heart rate, increased ventricular preload or afterload, and isoproterenol. Circulation 35 32, 1967

Bristow J D Crislip, R. L., Farrehi, C., Harris, W E., Lewis, R. P Sutherland, D W & Griswold, H. E. Left ventricular volume measurements in man by thermodilution. J clin. Invest. 43 1015 1964

Bristow J D Kloster, F E., Farrehi, C., Brodeur M. T H., Lewis, R. P & Griswold, H. E. The effects of supine exercise on left ventricular volume in heart disease. Amer Heart J 71 319 1966.

Bristow J D., Porter, G. A., Kloster F E. & Griswold, H. E. Hemodynamic changes attending angiocardiography Radiology 88 939 1967

Brockenbrough, E. C. & Braunwald, E. A new technic for left ventricular angiocardiography and transseptal left heart catheterization. Amer. J Cardiol. 6: 1062, 1960.

Brodén, B Hanson, H. E. & Karnell, J Thoracic aortography Preliminary report. Acta radiol. 29: 181 1948

Brown, A K., Epstein, E. J Coulshed, N Clarke, J M. & Doukas, N G. Hemodynamic changes after angiocardiography Brit. Heart J 31 233, 1969

Brown, R., Rahimtoola, S. H., Davis, G D & Swan, H. J C. The effect of angiocardiographic contrast medium on circulatory dynamics in man. Cardiac output during angiocardiography Circulation 31. 234, 196.

Bruns, H. A. Probleme der sogenannten quantitativen Angiokardiographie. Fortschr. Röntgenstr 113. 405 1970

Brunton, T L On the use of nitrite of amyl in angina pectoris. Lancet 2: 97 1867

Burch, G E., Giles, T D & Colcolough, H. L. Pathogenesis of "rheumatic" heart disease: critique and theory Amer Heart J 80 556, 1970

Burch, G. E., de Pasquale, N P Sun, S. C., Hale, A. R. & Mogabgab, W J Experimental coxsackievirus endocarditis. J Amer med. Ass. 196. 349 1966.

Burrows, B., Harrison, R. W Adams, W. E., Humphreys, E. M., Long, E. T & Reimann, A. F The post pneumonectomy state Amer J Med. 28 281, 1960.

Cabrera, E. & Monroy J R. Systolic and diastolic loading of the heart. Amer Heart J 43 661 1952.

Calderón, J Cineangiocardiographic diagnosis of aortic insufficiency Angiology 18 723 1967

Campbell, M. & Shackle, J W A note on aortic valvular disease with reference to etiology and prognosis. Brit. med. J 1 328, 1932.

Carleton, R. A. Change in left ventricular volume during angiocardiography Amer. J Cardiol. 27 460, 1971.

Carleton, R., Bowyer A. & Graettinger J Critique of left ventricular volume measurement by indicator dilution. Clin. Res. 13 203, 1965

Carleton, R. A., Bowyer, A. F & Graettinger J S Overestimation of left ventricular volume by the indicator dilution technique. Circulat. Res. 18 248, 1966.

Carleton, R. A. & Clark, J G. Left ventricular function during angiocardiography Amer. J med. Sci. 257 81, 1969

Carter, J B., Sethi, S Lee, G B. & Edwards, J E. Prolapse of semilunar cusps as causes of aortic insufficiency Circulation 43 922, 1971

Castellanos, A. & García, O The diagnosis of aortic insufficiency in the living subject and the cadaver by means of retrograde aortography Rev cuba. Pediat. 25 455 1953

Castellanos, A. & Pereiras, R. Counter-current aortography Rev cuba. Cardiol. 2: 187 1939-40.

Chapman, C. B., Baker, O Reynolds, J & Bonte, F J Use of biplane cinefluorography for measurement of ventricular volume. Circulation 18 1105 1958.

Charnoff, J & Silver A. The coexistence of rheumatic and arteriosclerotic heart disease in patients over the age of 40 years. Amer. Heart J 42: 809 1951.

Chatterjee, K., Sacoor M., Sutton, G C. & Miller, G A. H. Assessment of left ventricular function by single plane cineangiographic volume analysis. Brit. Heart J 33 565 1971

Chiche, P Maurat, J-P Joly J & Carlotti, J Les grandes insuffisances aortiques à évolution maligne. Sem. Hôp. Paris 37 2641 1961

Clark, W S., Kulka, J P & Bauer, W Rheumatoid aortitis with aortic regurgitation. Amer J Med. 22: 580, 1957

Cleland, W P Goodwin, J F Bentall, H. H., Oakley C. M., Melrose, D G & Hollman, A. A decade of open heart surgery Lancet 1. 191 1968

Coel, M. N. & Lasser, E. C. A pharmacologic basis for peripheral vascular resistance changes with contrast media injections. Amer. J Roentgenol. 11 802, 1971.

Cohn, L. H., Mason, D. T Ross, J J Morrow A. G. & Braunwald, E. Preoperative assessment of aortic regurgitation in patients with mitral valve disease. Amer J Cardiol. 19: 177 1967

Coleman, E. H. & Soloff, L. A. Incidence of significant coronary artery disease in rheumatic valvular heart disease. Amer. J Cardiol. 25: 401, 1970.

Colvez, P Alhomme, P Samson, M. & Guedon, J La pression de remplissage du ventricule gauche dans les grandes insuffisances aortiques. Ses relations avec l'allongement de la conduction auriculo-ventriculaire. Arch. Mal. Coeur 52: 1369 1959

Committee report of the American Heart Association and the Cardiac Society of Great Britain and Ireland: Standard method for taking and recording blood pressure readings, J.A.M.A. 113: 294 1939

Comroe, J H., Forster R. E., Dubois, A. B Briscoe, W A. & Carlsen, E. The lung. 2nd ed. Year Book Medical Publishers. Inc., Chicago, 1964

Conn, H. L., Jr., Helman, D. F Blakemore, W S., Kuo, P T & Langfeld, S B "Left heart" radiopotassium

dilution curves in patients with rheumatic mitral valvular disease. Circulation 15 532, 1957
Cooley D A., Bloodwell, R. D Hallman, G. L. & Jacobey J A., Aneurysm of the ascending aorta complicated by aortic valve incompetence. Surgical treatment. J cardiovasc. Surg. 8 1 1967
Cope, C., Technique for transseptal catheterization of the left atrium: preliminary report. J Thorac. Surg. 37 482, 1959
Corrigan, D J On permanent patency of the mouth of the aorta, or inadequacy of the aortic valves. Edinb Med and Surg. J 37 225, 1832.
Criscitiello, M. G Ronan, J A., J Besterman, E. M. M & Schoenwetter, W Cardiovascular abnormalities in osteogenesis imperfecta. Circulation 31. 255, 1965
Cullhed, L. Aortic stenosis Almqvist & Wiksell, Uppsala 1964
Cullhed, L, Michaëlsson, M. & Wranne, B Standardiserа blodtrycksmanschetterna! Läk Tidn. 65 1724 1968
Currens, J H., Thompson, W B Rappaport, M. B. & Sprague, H. B., Clinical and phonocardiographic observations on the Flint murmur. New Engl. J Med. 48 583, 1953
Davidson, P Baggenstoss, A. H Slocumb C. H. & Daugherty G. W Cardiac and aortic lesions in rheumatoid spondylitis. Proc. Mayo Clin. 38. 427 1963
Davila, J C. & Sanmarco M. E., An analysis of the fit of mathematical models applicable to the measurement of left ventricular volume. Amer J Cardiol. 18 31, 1966.
Degeorges, M. & Delzant, J.-F Elements de pronostic de l'insuffisance aortique isolée recueillis chez 206 malades agés de moins de 50 ans. Sem. Hôp. Paris 42, 1171 1966.
Dein, N. A., Ekeström, S. A. & Johansson, L Measurement of aortic regurgitation at operation. Acta Chir Scand 2. 44, 1966.
Delius, W & Enghoff, E., Studies of the central and peripheral hemodynamic effects of amyl nitrite in patients with aortic insufficiency Circulation 42· 787 1970.
Delius, W & Erikson, U Effect of contrast medium on blood flow and blood pressure in lower extremities Amer J. Roentgenol. 107· 869 1969
Demany M. A. & Zimmerman, H. A. Marked aortic regurgitation without peripheral vascular signs. Dis. Chest. 49· 61, 1966.
Desmond, E. G., Larsen, W E., Johnson, W B. & Kittle, C. F Post-traumatic aortic insufficiency occurring in Marfan syndrome, with attempted repair with plastic valve. New Engl. J. Med. 256 8 1957
Dodge, H. T & Baxley W A., Hemodynamic aspects of heart failure. Amer J Cardiol. 22: 24, 1968
Dodge, H. T & Baxley W A., Left ventricular volume and mass and their significance in heart disease. Amer J Cardiol. 23 528 1969
Dodge, H T Hay R. E. & Sandler, H., An angiocardiographic method for directly determining left ventricular stroke volume in man. Circulat. Res. 11 739 1962.
Dodge, H. T Sandler H Ballew D W & Lord, J D Jr The use of biplane angiocardiography for the measurement of left ventricular volume in man. Amer Heart. J 60· 762, 1960.
Dodge, H. T Sandler, H., Baxley W A & Hawley R. R.: Usefulness and limitations f radiographic methods for determining left ventricular volume. Amer. J Cardiol 18 10, 1966.
Dodge, H. T & Tannenbaum, H L., Left ventricular volume in normal man and alterations ith disease. Circulation 14 927 1956.
Downing, S. E. & Sonnenblick, E. H., Cardiac muscle mechanics and ventricular performance· Force and time parameters. Amer J Physiol. 207 705 1964
Dressler W & Rubin, R Complex shape and variability of the diastolic murmur of aortic regurgitation. Amer J Cardiol. 18 616, 1966.
Duroziez, P Du double souffle intermittent crural, comme signe de l'insuffisance aortique. Arch. gén Méd. 1 417 1861
Edwards, J E The congenital bicuspid aortic valve Circulation 23 485, 1961.
Eie, H The importance of cineangiography in the hemodynamic study of aortic valvular disease Universitetsforlaget, Oslo 1970
Eilers, R. J Notification of final adoption of an international method and standard solution for hemoglobinometry specifications for preparation of standard solution. Blood 29· 282, 1967
Ekelund, H., Enocksson, E., Michaelsson, M & Vom, H The incidence of acute rheumatic fever in Swedish children 1952–1961. Acta med. scand, 181 89 1967
Ekelund, L. G & Holmgren, A. Central hemodynamics during exercise. Circulat. Res. 20 33, 1967
Eliot, R. S. The adult forms of heart disease often confused with rheumatic endocarditis. Radiologic Clinics of North America 6. 399 1968.
Eliot, R. S. & Mork, J N Aortic regurgitation past 50 Geriatrics 22: 90, 1967
Eliot, R. S Woodburn, R. L. & Edwards, J E Conditions of the ascending aorta simulating aortic valvular incompetence. Amer J Cardiol 14 679 1964
Endrys, J & Bártová, A., Pharmacological methods in the phonocardiographic diagnosis of regurgitant murmurs. Brit Heart J 24 207 1962.
Endrys, J Belobrádek, Z., Petrie, M & Steinhart, L., Diagnosis of dominant mitral stenosis or regurgitation using amyl nitrite. Brit Heart J 26 250, 1964
Endrys, J & Steinhart, L Transseptal catheterization and carboangiography of the left heart by percutaneous route through the femoral vein. Cardiologia 41 47 1962
Enghoff, E. & Enghoff, H., Zur Technik der Gaswechselbestimmungen. Kungl. Svenska Vetenskapsakademiens handlingar 4 1, 1953.
Enghoff, E.: Unpublished data 1967
Enghoff, E. & Cullhed, L. Experiences with transseptal left heart catheterization. Amer Heart J 81 398, 1971.
Enghoff, H Apparat zur Gasanalyse. Acta med. scand. Suppl. 170· 307 1946.
Enghoff, H.: Quantitative Hämoglobinbestimmungen und

Sammarco, M. E., Fronek, K., Philips, C. M. & Davila, J. C. Continuous measurement of left ventricular volume in the dog. II. Comparison of washout and radiographic technics with the external dimension method. Amer. J. Cardiol. 18: 584, 1966.

Sepru, R. P. Taylor S. H. & Donald, K. W. Comparison of the pulmonary wedge pressure with the left ventricular end-diastolic pressure in man. Clin. Sci. 34: 125, 1968.

Sarewitz, A. B. & Mueham, G. E. Aortic insufficiency simulating combined aortic stenosis and insufficiency. Dis. Chest. 48: 291, 1965.

Sarnoff, S. J. & Berglund, E. Ventricular function. I. Starling law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 9: 706, 1954.

Savilahti, M. On the normal and the pathological PQ time of the electrocardiogram. Acta med. scand. 123: 252, 1946.

Schad, N., Stucky, J. P. & Wellauer, J. Das intermittierende phasengesteuerte Kontrastmittelinjektion in das Herz. Fortschr. Röntgenstr. 102: 619, 1965.

Schilder, D. P., Harvey, W. P. & Hufnagel, Ch. A. Rheumatoid spondylitis and aortic insufficiency. New Engl. J. Med. 255: 11, 1956.

Schlemming, G., Schemer, J. & Mäldner, J. Herzvolumen und Leistungsfähigkeit bei normaler und pathologischer Hämodynamik. Arch. Kreisl.-Forsch. 57: 273, 1968.

Schölmerich, P. Biographische Aspekte der entzündlichen Klappeninsuffizienz. Verh. dtsch. Ges. Kreisl.-Forsch. 31: 165, 1965.

Scott, R. C., Seiwert, V. J., Simon, D. L. & McGuire, J. Left ventricular hypertrophy. A study of the accuracy of current electrocardiographic criteria when compared with autopsy findings in one hundred cases. Circulation 11: 89, 1955.

Segal, J., Harvey, W. P. & Hufnagel, Ch. A. A clinical study of one hundred cases of severe aortic insufficiency. Amer. J. Med. 21: 200, 1956.

Segal, J., Harvey, P. & Corrado, M. The Austin Flint murmur: its differentiation from the murmur of rheumatic mitral stenosis. Circulation 18: 1025, 1958.

Segal, B. L., Likoff, W. & Kasper, A. J. "Silent" rheumatic aortic regurgitation. Amer. J. Cardiol. 14: 628, 1964.

Seldinger, S. I. Catheter replacement of the needle in percutaneous arteriography. Acta radiol. 39: 368, 1953.

Sellers, R. D., Levy, M. J., Amplatz, K. & Lillehei, C. W. Left retrograde cardioangiography in acquired cardiac disease. Amer. J. Cardiol. 14: 437, 1964.

Selzer, A., Naruse, D. Y., York, E., Kahn, K. A. & Matthews, H. B. Electrocardiographic findings in concentric and eccentric left ventricular hypertrophy. Amer. Heart J. 63: 320, 1962.

Shine, K. I., DeSanctis, R. W., Sanders, C. A. & Austen, W. G. Combined aortic and mitral incompetence: clinical features and surgical management. Amer. Heart J. 76: 728, 1968.

Stevens, J. & Hall, P. Incidence of acute rheumatic fever. Brit. Heart J. 33: 833, 1971.

Simpson, J. A., Jamieson, G., Dickhaus, D. W. & Grover, R. F. Effect of size of cuff bladder on accuracy of measurement of indirect blood pressure. Amer. Heart J. 70: 208, 1965.

Sjöstrand, T. Changes in the respiratory organs of workmen at an ore smelting works. Acta med. scand. Suppl. 196: 687, 1947.

Sjöstrand, T. Bestämning av den fysiska arbetsförmågan såsom klinisk undersökningsmetod. Läk. Tidn. 47: 349, 1950.

Sjöstrand, T. Volume and distribution of blood and their significance in regulating the circulation. Physiol. Rev. 33: 202, 1953.

Sjöstrand, T. Electrocardiography. In T. Sjöstrand (Ed.): Clinical physiology. Svenska bokförlaget. Stockholm 1967.

Skjaeggestad, O. & Kierulf, P. The electrocardiographic diagnosis of left ventricular hypertrophy. Acta med. scand. 185: 539, 1969.

Smith, Ph. W., Cregg, H. A. & Klassen, K. P. Diagnosis of mitral regurgitation by cardioangiography. Circulation 14: 847, 1956.

Söderholm, B., Theilesen, O., Heyman, F., Malmcrona, R. & Björntorp, P. Myocardial infarction in the younger age groups. III. Follow-up observations with special reference to exercise tolerance tests. Acta med. scand. 172: 585, 1962.

Sokoloff, L. Cardiac involvement in rheumatoid arthritis and allied disorders: Current concepts. Mod. Conc. cardiovasc. Dis. 33: 847, 1964.

Sokolow, M. & Lyon, T. P. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Amer. Heart J. 37: 161, 1949.

Soulié, P., Degeorges, M., Acar, J., Foucault, J.-P. & Baculard, P. L'angor des insuffisances aortiques, son traitement chirurgical. Soc. Méd. Hôp. Paris 114: 663, 1964.

Spagnuolo, M., Kloth, H., Taranta, A., Doyle, E. & Pasternack, B. Natural history of rheumatic aortic regurgitation. Circulation 44: 368, 1971.

Stapleton, J. F. & Harvey, W. P. A clinical analysis of aortic incompetence. Postgrad. Med. 46: 156, 1969.

Steiner, R. E. & Ekman, A. Radiological contrast studies of the left heart. Brit. J. Radiol. 35: 540, 1962.

Stewart, G. N. Researches on the circulation time and on the influences which affect it. IV. The output of the heart. J. Physiol. 22: 159, 1897.

Stigbrand, T. Molar absorbency of cyanmethaemoglobin. Scand. J. clin. Lab. Invest. 20: 252, 1967.

Storstein, O. Etiology of aortic valvular disease. Acta med. scand. 185: 17, 1969.

Storstein, O. & Wessler, E. Rheumatoid spondylitis and aortic insufficiency. Acta med. scand. 165: 125, 1959.

Strandell, T. Circulatory studies on healthy old men. Acta med. scand. Suppl. 414, 1964.

Strandell, T. Phonocardiography. In T. Sjöstrand (Ed.): Clinical physiology. Svenska bokförlaget. Stockholm 1967.

Ström, G. Recommended symbols, nomenclature and criteria for certain measures of physical capability. Försvarsmedicin 3: 159, 1967.

Ström, G. & Werkö, L. Rekommendationer för mätning

av arteriella blodtrycket med manschett-metoden. Läk. Tidn. 55 35 1958.

Segawa, M., Okada, R., Hiraoka, K., Ohkawa, S. & Shimada, H. A new etiological concept of the aortic regurgitation in the aged. Jap Heart J 10: 20, 1969

Soh, S. K Differentiation of the murmur of aortic regurgitation and pulmonary regurgitation with amyl nitrite. Circulation 22: 820, 1960.

Sutton, D Thoracic aortography in adults—clinical aspects. Brit. J Radiol. 33 545 1960.

Swan, H. J C. & Beck, W Ventricular nonmixing as source of error in the estimation of ventricular volume by the indicator-dilution technic. Circulat. Res. 8 989 1960.

Swan, H. J C., Knopp, T J & David, P R.. Effect of aortic mixing on determination of ventricular volumes by washout. Physiologist 8 284 1965

Symbas, P N Walter P F Hurst, J W & Schlant, R. C.. Fenestration of aortic cusps causing aortic regurgitation. J thorac. cardiovasc. Surg. 57· 464, 1969

Tambe, A. & Zimmerman, H. A.: Diseases of the aortic valve. Geriatrics 22 180, 1967

Taubman, J O Goodman, D J & Steiner, R. E.. The value of contrast studies in the investigation of aortic valve disease. Clin. Radiol. 17· 23, 1966.

Tenney, A. E. & Cook, J E.. The determination of the diastolic pressure in aortic regurgitation. Arch. intern. Med. 11 542, 1913

Thorén, C.. Cardiomyopathy in Friedreich ataxia. Acta paediat. Suppl. 153, 1964.

Thurn, P Kontrastmitteluntersuchung der Herzklappeninsuffizienz. Verh. dtsch Ges. Kreisl.-Forsch. 31 195, 1965

Tompsett, R.. Bacterial endocarditis. Arch. intern. Med. 119· 329 1967

Tompsett, R. & Lubash, G. D Aortic valve perforation in bacterial endocarditis. Circulation 23 662, 1961

Tyrrell, M. J Ellison, R. C., Hugenholtz, P G. & Nadas, A. S.. Correlation of degree of left ventricular volume overload with clinical course in aortic and mitral regurgitation. Brit. Heart J 32: 683, 1970.

Ueda, H., Sakamoto, T Kawai, N., Watanabe, H Uozumi, Z., Okada, R., Kobayashi, T Yamada, T Inoue, K. & Kaito, G The Austin Flint murmur Phonocardiographic and patho-anatomical study Jap. Heart J 6. 294, 1965.

Wahlund, H.. Determination of the physical working capacity Acta med. scand. Suppl. 215 1948.

Warner, H R.. Analysis of the role of indicator technics in quantitation of valvular regurgitation. Circulat. Res. 10· 519 1962.

Warner, H. R. & Toronto, A F Quantitation of backflow in patients with aortic insufficiency using an indicator technic. Circulat. Res. 6. 29 1958

Warner H. R. & Toronto, A F Effect of heart rate on aortic insufficiency as measured by dye-dilution technique. Circulat. Res. 9· 413, 1961.

Watanabe, H. & Sakamoto, T Clinical and phonocardiographic study of aortic regurgitation Jap. Heart J 2: 7 1961.

Weaver W F Edwards, J E. & Brandenburg, R. O Idiopathic dilatation of the aorta with aortic valvular insufficiency possible forme fruste of Marfan syndrome. Proc. Mayo Clin. 34 518 1959

Weed, Ch. L., Kulander B. G Mazzarella J A & Decker J L.. Heart block in ankylosing spondylitis Arch. intern. Med. 117 800 1966.

Weintraub A. M. & Zvaifler, N J The occurrence of valvular and myocardial disease in patients with chronic joint deformity Amer J Med 35 14 1963

Vendsborg, P Fabricius, L. & Olesen, K H Decreasing incidence of history of acute rheumatic fever in chronic rheumatic heart disease. Cardiologia 53 332, 1968.

de Verdier C.-H & Killander J Kliniska laboratorieundersökningar Pharmacia prep Uppsala 69 1971

Wiggers, C. J The magnitude of regurgitation with aortic leaks of different sizes J Amer med. Ass. 97 1359 1931

Wigle E. D & Labrosse, C. J Sudden, severe aortic insufficiency Circulation 32. 708, 1965

Wilcken, D E. L.. Left ventricular volume in man: the relation to heart rate and to end-diastolic pressure. Aust Ann. Med. 17· 195 1968

Wilson, M G. & Lim, W N.. The natural history of rheumatic heart disease in the third, fourth and fifth decades of life. Circulation 16. 700, 1957

Wood, P Diseases of the heart and circulation, 2nd ed., 3rd ed. Eyre and Spottiswoode, London 1956 and 1968.

World Health Organization. Techn. Rep Ser 168 11 1959

Wrabec, K., Lukasik, S. & Nowosad, H Zastosowanie azotynu amylu fenyloefrynu w diagnostyce fonokardiograficznej i osłuchowej niedomykalności aortalnej towarzyszącej zwężeniu mitralnemu. Pol. Arch Med Wewn 46 357 1971.

Wranne, B Circulatory adaptation early after pulmonary surgery Acta Univers. Upsal. Abstracts of Uppsala Dissertations in Medicine, 83 1970.

Wright, B M & McKerrow C. B. Maximum forced expiratory flow rate as measure of ventilatory capacity with description of new portable instrument for measuring it. Brit med. J 2: 1041, 1959

Yagasawa, T & Wakabayashi, A Clinical studies on ventricular function by left ventricular angiography Jap Circulat J. 33 1341, 1969

Zelis, R., Mason, D. T Spann, J F J & Amsterdam, E A.. The effects of angiographic dye on cardiac contractility and the peripheral circulation in man. Amer J. Cardiol 25 137 1970

Zimmerman, H. A.. Left ventricular pressures in patients with aortic insufficiency studied by intracardiac catheterization. J clin. Res 29· 1601, 1950.

Zimmerman, H. A., Scott, R. W & Becker, N O Catheterization of the left side of the heart in man. Circulation 1 357 1950

Zvaifler N. J & Weintraub, A. M.. Aortitis and aortic insufficiency in the chronic rheumatic disorders. A reappraisal. Arthr and Rheum. 6: 241 1963

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S. A.

CONTENTS

I INTRODUCTION

The major significance of coronary atherosclerotic changes is that these lesions, either alone or in association with an acute coronary occlusion, are a cause of myocardial ischaemia, which in turn is responsible for such clinical states as angina pectoris, sudden coronary death, acute coronary attack without necrosis, and myocardial infarction (MI).

A careful history an observed fever reaction, certain routine laboratory tests such as the white blood cell count and the erythrocyte sedimentation rate are sufficient for the diagnosis of MI in nearly fifty percent of cases. The electrocardiographic technique has provided much information concerning myocardial damage, and the rate of accuracy in confirming an infarct by this procedure approaches eighty percent or over (Pruitt et al. 1963, Woods et al. 1963 Simonson et al. 1966).

However fairly often additional confirmation is needed. The presenting symptoms are often atypical because of some other disease, or the patient may have one of the complications of MI, such as pulmonary oedema, congestive heart failure, cardiac arrhythmia or cerebral vascular attack. The disease is not always associated with characteristic pains (Roseman 1954, Pathy 1967) or it may be quite symptomless (Lindberg et al. 1960 Kannel et al. 1970). The situation mentioned last is, however seldom able to produce acute diagnostic problems, because it is in general not possible to examine these patients in the acute phase.

It is well known that there are MI patients with electrocardiograms not showing any expected diagnostic changes. A certain amount of myocardium must be necrotic before the electrocardiogram becomes diagnostic. Of even greater significance is the localization of infarction, because there are relatively «silent» areas in the myocardium, for example the back of the left ventricle, the high anterolateral wall, the cardiac apex, the papillary muscles, the right ventricle, or the atrium (Logue and Hurst 1966). The QRS changes do not develop if there is infarction of the subendocardial layer only. Previous infarctions may produce difficulties in the interpretation of electrocardiographic signs of later myocardial damages. Certain intraventricular conduction defects such as left bundle branch block may obscure the changes of MI.

In addition to this there are some other diseases that may produce electrocardiographic alterations simulating MI. Changes in patients with advanced emphysema or with left ventricular hypertrophy may mimic those of MI. A «dead-zone» effect may be a result of obstructive cardiomyopathy or of infiltrative diseases of the myocardium, such as amyloidosis, scleroderma, metastatic neoplasm or sarcoid of the heart. Pericarditis and digitalis medication may cause ST segment and T wave changes resembling early or subendocardial MI.

In patients with conditions simulating myocardial damage by electrocardiographic changes or by clinical features the exclusion

of MI requires additional diagnostic resources, as also does the confirmation of MI in cases that are not adequately verified by other means.

Only sixteen years have passed since LaDue, Wroblewski and Karmen (1954) published their original observation that serum aspartate aminotransferase was increased in patients with acute MI. In this relatively short span of time the enzymological aid in the diagnosis of MI has become a routine course of action. A multitude of enzyme tests have been recommended for this purpose, and the clinician may often find himself difficult in selecting the most suitable test or group of tests.

II REVIEW OF THE LITERATURE

A. Enzyme tests for confirmation of myocardial infarction

1. *Aspartate aminotransferase (ASAT)*

Aspartate aminotransferase, previously and here called *glutamic oxaloacetic transaminase* (GOT), participates in the aminoacid metabolism of the living cell. It occurs in most animal and human tissues, but its activity varies greatly in different organs. The greatest GOT activities have been observed in both the heart and the liver i.e. 7000—8000 times that in normal serum. A considerable activity is present also in skeletal muscle, i.e. 5000 times that in normal serum (Batsakis and Briere 1967 a)

On the basis of some experimental and clinico-pathological works it is suggested (Wroblewski 1963) that at least a part of the mechanism of elevation of serum GOT activity — and that of some other serum enzyme — after MI or any other tissue damage is the release of intracellular enzyme into the extracellular compartment owing to necrosis of cells or to loss of integrity of cellular membrane.

GOT like other serum enzymes, is in practical work measured in terms of its activity i.e as the rate at which it catalyzes a certain chemical reaction. Many factors, however other than the specific tissue injury and the manner of enzyme assay act on the measurable serum enzyme activity (Baron 1963), such as catabolism, excretion of enzyme, inhibitors, activators and cofactors, which mostly are matters relatively little known.

Abnormal levels of serum GOT activity are usually found twelve hours after the onset of MI (Coodley 1965) The mean value of its peak activity is about four times that of normal serum and is reached before thirty six hours after the incident. The return to normal level occurs by the fourth day after MI (Batsakis and Briere 1967 a) Numerous clinical and experimental studies have been published concerning the usefulness of this test in the diagnosis of MI, as reviewed extensively by Agress (1959). This author gave a summary of 1235 patients with clinically proved MI, and in 97 percent of these patients the serum GOT activity exceeded the upper limit of normal. According to West and his co-workers (1966) the incidence of abnormal serum GOT levels in patients with autopsy proved infarction approached 100 percent, particularly if the enzyme measurement had been performed at least twice between the twelfth and the forty-eighth hour after the onset of MI.

According to the varying grounds on which MI and coronary insufficiency are diagnosed, different figures have been reported for the frequency of abnormal GOT values in patients with coronary attacks not associated with recognized myocardial necrosis (Proger and Naimi 1963). In the studies reported in the reviews mentioned above the percentage of abnormal GOT results did not exceed 10 in such patients. Resnik (1962) however reported a number of patients of his own and surveyed other studies (Nydick et al. 1957 Goble and O'Brien 1958) all con

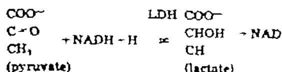
cerning preinfarction angina, a term used synonymously with coronary insufficiency and most of the reported patients had elevated serum GOT values and so late as on the fourth to tenth day after the onset of substernal pain.

Abnormalization frequencies of GOT activity varying between 3—40 per cent have been reported in patients with congestive heart failure not accompanied by acute MI (Agress 1959 Konttinen and Halonen 1962, West et al. 1966, Batsakis and Briere 1968 Crowley 1968) In patients with pulmonary infarction or embolism slightly elevated GOT values have been observed in 14—50 percent of cases (Agress 1959 Stevens and Burdette 1964 Vincent and Rapaport 1965, West et al. 1966, Sasahara et al 1967 Coodley 1969) Deviating from these results, no abnormalizations of GOT were seen in patients with pulmonary embolism by LaDue et al. (1954) and by Wacker et al. (1961).

The highest GOT values have been observed in acute hepatocellular lesions (Wroblewski and LaDue 1956 a, Henley et al. 1959, Gelb et al. 1962 Wilkinson 1962, Zimmerman and West 1963). Slight rises have been reported after strenuous exercise (Garbus et al. 1964 Swaiman and Awad 1964).

2 *Lactate dehydrogenase (LDH)*

Soon after the introduction of the serum GOT test into clinical use another enzyme, serum lactate dehydrogenase was observed to increase in acute MI This is an enzyme of the glycolytic cycle catalyzing reversibly the conversion of pyruvate to lactate. It utilizes nicotinamid-adenine dinucleotide (NADH, formerly known as diphosphopyridine nucleotide DPNH) as a coenzyme for the reaction



LDH activity occurs to a variable extent in all human tissues, in the liver and skeletal muscle there is a clearly higher LDH content than in the heart, and the LDH content of normal erythrocytes is about 1000 times that of normal serum (Batsakis and Briere 1967 a)

Wroblewski and LaDue (1955) were again the first to report their experiences in the clinical use of this enzyme test in the diagnosis of MI. The LDH test has been assumed to be superior to GOT in the first place because of the longer duration of abnormal activities of the first named enzyme after the onset of infarction (Wacker et al 1956, White 1956, Rosalki 1963 b Nissen et al. 1965 Kibe and Nilsson 1967) The mean time for which abnormal LDH values are observed is about eight days (Elliot and Wilkinson 1962) The mean peak LDH activity after MI is about 3—4 times the upper normal limit (Batsakis and Briere 1967 a) and it is reached about seventy two hours after the onset of infarction.

The preliminary works were followed by publication of further experiences (Zimmerman and Weinstein 1956 West et al. 1961 Elliot et al. 1962, Wroblewski 1963, Strandjord and Clayson 1966 b) showing that slightly elevated serum LDH activities are observable in nearly every other patient with congestive heart failure without acute MI. The high LDH content of liver tissue makes it still better explicable that abnormal values of this enzyme are commonly measured in patients with acute liver cell lesions (Elliot and Wilkinson 1961 Konttinen 1961 Konttinen and Halonen 1962, Rosalki 1963 b)

Transient elevation of LDH has been observed after strenuous exercise (Halonen and Konttinen 1962, Garbus et al. 1964) and after traumatic lesions of skeletal muscle (Konttinen et al. 1969).

More divergent are the reports concerning the alterations of serum LDH activity in patients with pulmonary embolism. Amador and Potchen (1966) reported their own work and gave a survey of seven earlier investiga-

tions according to which the LDH test has a nearly 100 per cent diagnostic accuracy rate for confirmation of pulmonary embolism, and the authors recommended LDH measurement as a screening test for this condition. It was stated by these authors that diseases or states predisposing to pulmonary embolism, such as congestive heart failure, trauma and the postoperative state, do not give rise to serum LDH activity elevations. However less benefit has been derived from this test in the diagnosis of pulmonary embolism by other workers (Rosalki 1963 b Levine et al. 1964 West et al. 1966 Batsakis and Briere 1968 Sasahara et al. 1967 Polachek et al. 1968 Auvinen and Konttinen 1971).

Augmentation of serum LDH activity has likewise been reported during circulatory shock caused also by conditions other than MI (Shubin and Weil 1963 Konttinen et al. 1964) in patients with neoplastic disease (Wroblewski and Gregory 1961) and in certain haemolytic states (Palohelmo and Ikkala 1965)

3. *Lactate dehydrogenase isoenzymes*

a. *Electrophoretic isoenzyme estimation.* Even though the original LDH test still is one of the most commonly used enzymatic diagnostic tools of MI, attempts have been made to improve its specificity The discovery that the lactate dehydrogenase of various human and animal tissues can be separated by electrophoresis into several, at the most five fractions has resulted in diagnostic applications of these fractions (Sayre and Hill 1957 Vesell and Bearn 1957 Wieland and Pfleiderer 1957), called isoenzymes (Wieme 1959). Later investigations have proved that each of the five LDH isoenzymes is a tetramer composed of two monomers, H and M (Markert 1963, Wilson et al. 1963). They have five varying possibilities to form tetramers, i.e. intact enzyme molecules. The combinations HHHH and HHHM form the fast migrating or anodic isoenzymes LDH_1 and LDH_2, which predominate in heart muscle. The tetramer MMMM is conversely the cathodic, slowest migrating isoenzyme LDH_5 occurring in high contents in the liver and skeletal muscle. The two remaining combinations, HHMM and HMMM, form the isoenzymes LDH_3 and LDH_4 with intermediate electrophoretic mobility Genetic evidence has been obtained that the synthesis of the two subunits H and M is directed by two different structural genes (Kraus and Neely 1964).

For the separation of LDH isoenzymes numerous electrophoretic methods and modifications have been employed, using varying buffer solutions, supporting media and other physical factors (Wieland et al. 1959 Wieme 1959 Pfleiderer and Wachsmuth 1961 Barnett 1962, Goldberg 1963 Barnett 1964 Preston et al. 1965 a, Wieme 1965 1966)

For the determination of individual isoenzymes after their movement apart in electrophoresis, the isoenzymes were at first eluted from the supporting medium with the corresponding fractions of other serum proteins, and the LDH activity of each fraction was measured by conventional assay methods. This procedure is still being used when a high degree of precision is required. The elution, however is time-consuming for clinical use, and quicker staining techniques have been introduced. Originally they were developed for the cytochemical localization of enzymes (Pearse 1960) but have since found applications in the detection of isoenzymes after electrophoresis.

The tetrazolium salts, and at present mostly nitro blue tetrazolium and p-iodonitro-tetrazolium violet readily undergo reduction to coloured formazans at the expense of NADH2 which is produced in the backward reaction from lactate to pyruvate, with methylphenazonium methosulphate as the hydrogen-transferring agent. With suitable techniques a roughly quantitative assessment of the relative activities of the various LDH

isoenzymes can be obtained (Markert and Møller 1959 van der Helm 1962, Latner and Turner 1967)

There are considerable discrepancies between the normal distributions of LDH isoenzymes presented by different workers (Roman 1969) in spite of the similar methods used by them for isoenzyme separation and estimation. Thus the quantitation of LDH isoenzymes by the poorly reproducible methods so far available is indeed only approximate (van der Helm et al. 1962, Lauryssens et al. 1964 Cohen and Larson 1966, Wright et al. 1966 Bohn and Nissen 1967 Dietz and Lubrano 1967 Jordan and White 1967 Papadopoulos and Kintzios 1967 Muggli 1968).

The normal pattern of serum LDH isoenzymes has its origin in the gradual release of isoenzymes from various tissues, especially the blood cells, liver and skeletal muscle (Batsakis and Briere 1967 c) An increased leakage of LDH from a damaged tissue as occurs in MI, will impress the pattern of this tissue on the normal serum distribution of LDH isoenzymes (Wroblewski and Gregory 1961)

The heart pattern mentioned above is imitated by that of erythrocytes and the kidney (Wroblewski and Gregory 1961 Roman 1969) LDH_5 predominates in some malignant tissues, thus mimicing the situation in the liver and skeletal muscle (Cohen et al. 1964) Although the most prominent LDH isoenzyme in the lung is LDH_3 (Wroblewski and Gregory 1961), various patterns have been observed in the sera of patients with pulmonary embolism or infarction (van der Helm et al. 1962, Cohen et al. 1966 Batsakis and Briere 1966, Muggli 1968 Coodley 1969)

It is generally supposed that the determination of isoenzymes will clearly improve the poor specificity of the total LDH assay Excluding some pessimistic conclusions drawn by a few workers concerning the sensitivity of LDH isoenzymes in the confirmation of MI (Bohn and Nissen 1967 Hosty and Noto 1968), the results have been promising even if the idea of a biochemical biopsy» has been an over-estimation produced by the early enthusiasm.

In view of the imperfection of performance and especially of the tedious and time-consuming techniques of isoenzyme fractionation, it is understandable that LDH electrophoresis has not become a routine method in clinical laboratories, and simpler procedures have been worked out with the object of improving the specificity of the LDH test.

b. *Isoenzymes by differential affinity to substrate (alpha hydroxybutyrate dehydrogenase HBD).* In addition to pyruvate LDH has been observed to reduce a variety of other alpha ketoacids, but only against alpha-oxobutyrate does its activity compare with that against pyruvate (Meister 1950) It has been demonstrated that there is a marked difference in the relative activities with pyruvate and alpha-oxobutyrate between the fast and slow moving LDH isoenzymes (Rosalki and Wilkinson 1960), so that LDH_1 and LDH_2 use alpha-oxobutyrate as substrate more readily than do LDH_4 and LDH_5 (Plummer et al. 1963 a) The components active against alpha-oxobutyrate have been called HBD even though it apparently does not form any distinct enzyme entity (Hansson 1962, Rosalki 1963 a) The HBD activity has never been detected unaccompanied by LDH activity

As was to be expected, elevated HBD activities have been observed in conditions associated with an increased release of LDH_1 and LDH_2 isoenzymes into the serum, as in MI (Elliot et al. 1962, Hansson et al. 1962, Konttinen and Halonen 1962 Pagliaro and Notarbartolo 1962, Bigazzi and Ciampi 1963, Rosalki 1963 b Preston et al. 1964 Coodley 1968 a) in myocarditis (Elliot et al. 1962) and after cardiac surgery (Pyörälä et al. 1963). Haemolytic states, certain anaemias and blood samples haemolyzed from technical

causes result in elevated HBD values (Elliot and Wilkinson 1963 Wilkinson 1965)

In addition to a slightly better sensitivity a longer duration of abnormal activities of serum HBD compared with serum LDH, has been demonstrated by the workers mentioned above in connection with MI. It has been stated, that serum HBD is not elevated in patients with angina pectoris or coronary insufficiency (Konttinen 1961, Rosalki 1963 b)

In early reports the specificity of the HBD test for heart damage was valued at a high degree (Elliot et al. 1962, Elliot and Wilkinson 1963) but with gaining clinical experience the specificity of this test was observed to be only a relative one (Konttinen and Halonen 1962, Preston et al. 1964 Stuart et al. 1965) Wilkinson (1962, 1965) has emphasized the significance of the HBD/LDH ratio for the differentiation of MI from other disorders in which elevated HBD values are observed, as from congestive heart failure and primary hepatobiliary diseases. This ratio has not, however been found helpful in differential diagnosis by other workers (Rosalki 1963 b Preston et al. 1964 Nissen et al. 1965, Dube et al. 1968)

Even if it is generally accepted that the HBD level is a better indicator of myocardial damage than the total LDH activity some evidence has been acquired that HBD measurement does not specifically reflect only the fast moving or »cardiac» isoenzymes, but that LDH_2, LDH_3 and even LDH_4 have a notable HBD activity too (Strandjord and Clayson 1966 b). Methods have been developed which after inactivation of the non-cardiac fractions measure only the »cardiac» isoenzymes.

c. *Isoenzyme estimation by heat inactivation (H LDH)* It has been observed that the LDH isoenzymes with slow electrophoretic mobility LDH_4 and LDH_5, are less stable than the fast moving fractions when exposed to elevated temperatures (Hill 1958, Plagemann et al. 1961 Plummer and Wilkinson 1963 Karl and Peters 1967) This difference in heat sensitivity has been employed as a means of assessing the relative amounts of LDH_1 and LDH_5 in an abnormal serum LDH and several methods have been recommended for clinical purposes.

Strandjord with his co-workers (1961 1962, 1966 a) has presented a heat stability test in which the heat stable component is the LDH activity remaining after incubation of buffered sera at 65 C for 30 minutes. Further it has been proved that the heat stable fraction estimated by this method reflects specifically the LDH_1 isoenzyme determined after electrophoretic separation of serum LDH. It is worth mentioning that LDH_1 is the isoenzyme that increases most in the sera of patients with acute MI (Wroblewski and Gregory 1961). The heat stable LDH. total LDH ratio, expressed as a percentage, was about 50 per cent in patients with acute MI and below 10 per cent in patients with infectious hepatitis (Strandjord and Clayson 1961). The heat stability of LDH fractions isolated by means of chromatography was measured by Dioguardi et al. (1963) by a method similar to that reported here.

Other modifications with a single incubation temperature, 58—60 C, are those presented by Latner and Skillen (1963), Bell (1963), Peters and Davis (1969) and Reynoso et al. (1969).

Attempts have been made to separate serum LDH isoenzymes into three fractions by using two temperatures for incubation before LDH measurement. According to the original two step» procedure (Wroblewski and Gregory 1961), samples of serum to which coenzyme has been added are heated 30 minutes at 57 or 65 C, after which the LDH activity remaining in each sample is compared with that in an unheated sample. In addition to the heat stable fraction, which is the LDH activity of the sample heated at 65 C and represents LDH_1 one can estimate the heat labile fraction corresponding to LDH_5, which is the difference

between the activities of the unheated sample (total LDH) and that heated at 57°C. The isoenzymes with an intermediate heat stability LDH_2, LDH_3 and LDH_4, have an activity of the size of the difference between the activities in samples heated at 57 C and 65 C. This procedure has been applied to the clinical diagnosis of MI by Dubach and von Orelli (1963) and Schneider et al. (1966). Two to three step methods, presented by Wüst et al. (1962) and Roman et al. (1969) comprise temperatures and incubation times modified from the above described original method.

The authors reporting their experiences of the heat stability test consider it a useful means of excluding the unspecific causes of elevated serum LDH values in patients with suspected MI. The more complex procedures, however with the object of separating serum LDH into more than two fractions by heat inactivation, are still too difficult for many clinical laboratories and too little is known about the correlation between the clinical states and the activity of LDH in those fractions.

d. *Isoenzyme estimation by urea inactivation (U LDH).* In connection with the investigations of the chemical composition of LDH isoenzymes it was observed that high concentrations of urea may split all isoenzyme tetramers into the four monomers mentioned above (Appella and Markert 1961 Cahn et al. 1962, DiSabato and Kaplan 1965) In low concentrations of urea the isoenzymes differ in their sensitivity to inactivation, i.e., the slower the electrophoretic mobility of the isoenzymes, the greater their inactivation. This competitive inhibition can be used for differentiation between fast and slow moving isoenzymes of LDH (Richterich et al 1962, Plummer et al 1963 b Richterich and Burger 1963) Withycombe with his co-workers has demonstrated (1965) that in 2M urea it is possible to distinguish LDH_1 and LDH isoenzymes from LDH and LDH fractions, since the latter are completely inhibited while the former retain about 80 per cent of their original activity provided that pyruvate is used as substrate. One of the first reports of the usefulness of the urea inhibition test in the diagnosis of MI was that published by Emerson and Wilkinson (1965).

In this laboratory the subject has been studied by Konttinen and Lindy (1965, Lindy and Konttinen 1966 a and b). In developing their modification of the urea inhibition test they observed that NADH protects cardiac isoenzymes from urea inhibition without having this effect on non-cardiac fractions. In addition the separation of the isoenzymes was further improved by elevation of the substrate (= pyruvate) concentration. In their clinical evaluation this test (Lindy and Konttinen 1967 a and b) was appraised to give information about the cardiac isoenzymes comparable to that given by electrophoresis. The clinical appraisal of the test was continued later on (Auvinen and Konttinen 1971) Modifications of the urea inhibition test not differing in principle from those reported here have been presented by Hardy (1965) Emery et al. (1968) and Welshman and Rixon (1968)

LDH_1 and LDH_5 isoenzymes differ from each other also with respect to the optimal substrate concentration (Rosalki and Wilkinson 1960) A technique based upon this fact has been devised by Plagemann et al. (1960) for the determination of the relative proportions of the mentioned isoenzymes in a mixture of them. The same principle has been combined closely with the urea inhibition procedure (Babson 1967) resulting in the observation that the ratio of the LDH activity in 2M lactate to the LDH activity in 0.02M lactate-2M urea permits a good differentiation between heart and liver isoenzymes. The higher lactate concentration is observed to favour LDH_5 more than LDH_1 while the lower substrate concentration with urea inhibition is intended to reflect the heart isoenzymes By using the ratio of

activities or absorbances the use of confusing enzyme units is avoided.

Babson's method and its correlation with the electrophoretic isoenzyme estimation has been tested clinically (Dietz et al. 1968, Lubran and Jensen 1968, Batsakis and Briere 1969 Foy and King 1969) and it has been defined to be an additional laboratory test in the diagnosis of MI.

e. Rarely used methods for LDH isoenzyme estimation. In addition to the aforementioned methods, different physical and chemical properties of LDH isoenzymes have been utilized in procedures designed to allow estimation of the relative concentration of the two subunits H and M. These procedures have involved differences between isoenzymes in such characteristics as the reaction rate with coenzyme analogs (Kaplan and Ciotti 1961), the selective adsorption on DEAE-cellulose (Hess and Walter 1961, Richterich et al. 1963) immunological properties (Nisselbaum et al. 1961), solubility in 50 per cent acetone (Latner and Turner 1963) and effect of chemical inhibitors other than urea, as oxamate (Plummer and Wilkinson 1963) or oxalate (Emerson and Wilkinson 1965) However clinical experience with these procedures is still insufficient.

4. *Creatine kinase (creatine phosphokinase CPK)*

CPK catalyzes the reversible reaction ATP + creatine $\overset{CPK}{\rightleftharpoons}$ ADP + creatine phosphate. This enzyme is found principally in the so-called excitable tissues, i.e. skeletal muscle, heart and nervous tissue. The CPK content of skeletal muscle is about three times that of heart, and in cerebral cortex slightly lower activities have been observed than in heart (Oliver 1955 Tanzer and Gilvarg 1959 Hess et al. 1964, Dawson and Fine 1967) The fact that virtually undetectable amounts of CPK activity have been found in kidney liver lung and pancreatic tissues and not at all in red blood cells has resulted in diagnostic applications of this enzyme.

At first the CPK test was introduced in the differential diagnosis of certain primary muscular diseases (Ebashi et al. 1959) and numerous later investigations have been published on the subject (Pearson et al. 1961 Dreyfus and Schapira 1962) Dreyfus et al. were the first to use this test in the diagnosis of MI (1960) observing a distinct increase of this enzyme in the sera of patients with recent MI. This was confirmed by a number of others (Forster and Escher 1961 Colombo et al. 1962, Konttinen and Halonen 1963, Schneider and Heise 1963, Sörensen 1963 Nissen et al. 1965, Preston et al. 1965 b, Warburton et al. 1965 Vincent and Rapaport 1965). It was a common experience that the CPK activity in serum begins to rise on an average three to four hours after the onset of infarction, reaches the peak before thirty-six hours, and returns to normal levels by the second to fourth day after infarction.

It was observed, however that the original methods for CPK measurement, as that presented by Tanzer and Gilvarg (1959), had certain disadvantages. Most inconvenient was the necessity to perform the measurement of CPK activity within a few hours after venipuncture because of the loss of activity during storage of sera from patients with MI (Hughes 1962, Hess et al. 1964 Okinaka et al. 1964 Vincent and Rapaport 1965). The short activity span at abnormal levels after MI and the poor reproducibility of CPK results were also criticized.

Beginning with Ennor and Rosenberg (1954), a number of workers have observed an activating effect of sulfhydryl (SH) reagents on CPK activity (Chappell and Perry 1954 Oliver 1955 Cho et al. 1960 Mahowald et al. 1962, Duma and Siegel 1965 Kar and Pearson 1965 a, Forster 1967 Hess et al. 1968 Coodley 1968 a, Kierkegaard—Hansen and Kierkegaard—Hansen 1969). The common

opinion of most authors was that SH compounds enchance the CPK activity about fivefold, the rise to pathological values occurs sooner after MI, the activity span at abnormal levels becomes longer the reproducibility of results improves, and the apparent loss of activity can be eliminated by using methods with SH stimulation.

With the improving sensitivity of methods, however the usefulness of the SH activated procedures as indicator of myocardial damage has decreased (Velez—Garcia et al. 1966 Batsakis and Briere 1967 b, Crowley 1968) Even simple diagnostic and therapeutic measures, such as puncture of deep veins or arteries for angiographic study intramuscular injection, cardiac catheterization, etc., may cause elevation of SH-stimulated CPK activity This is explicable on the basis of the high content of this enzyme in skeletal and cardiac muscle mentioned earlier After severe and prolonged athletic training serum CPK values up to three times the upper limit of normal have been observed (Colombo et al. 1962, Griffiths 1966), but on the other hand the effect of muscular activity has been considered negligible in the case of suspected MI unless there has been very vigorous and prolonged physical activity by a relatively untrained person (Batsakis and Briere 1967 a).

Elevated CPK values have been measured in the sera of patients with hypothyroidism (Graig and Ross 1963, Graig and Smith 1965 Griffiths 1965 Doran and Wilkinson 1971) and of acutely intoxicated alcoholics (Nygren 1966)

Several attempts have been made to improve the specificity of the CPK test also by isoenzyme separation procedures (Deul and van Breeman 1964 Sjovall and Voight 1964 Griffiths 1965 Kar and Pearson 1965 b Rosalki 1965 van der Veen and Willebrands 1966, Graig and Smith 1967 Menache et al. 1968), but until now these determinations have been applied mostly to tissue extracts and they have not offered any information applicable to clinical cases. Recently a method has been reported allowing a quantitation of CPK isoenzymes in serum (Somer and Konttinen 1972) and the preliminary results of these studies on CPK isoenzymes in MI will be published (Konttinen and Somer 1972).

5 *Other enzyme tests suggested for confirmation of myocardial infarction*

Another enzyme termed muscle specific is *adenylate kinase* which is observed to occur in heart and skeletal muscle in concentrations higher than in other organs (Oliver 1955). Schreiber (1964) has tried it as a confirmatory test of MI with promising results. Later on it was demonstrated, however that activities of this enzyme comparable with those of heart and skeletal muscle occurred in many organs, such as brain, liver and kidney (Lehmann et al. 1966) Elevated levels of adenylate kinase activity were observed to occur even earlier after MI than those of CPK, but this advantage was lost with the finding that abnormal values of the first named enzyme occurred in most patients with diseases that should be differentiated from MI. Further more the practical utility of this test is nullified by its extreme sensitivity to haemolysis (Madritsch 1968).

Aldolase an enzyme used mostly in the diagnosis of muscle and liver diseases, has been determined also in the sera of patients with MI (West et al. 1966) It behaves very much like GOT in these cases, but erythrocytes normally contain more abundantly aldolase (150 times the normal serum activity) than GOT which means a disadvantage in its use for most clinical purposes (Batsakis and Briere 1967 b)

Malic dehydrogenase and *phosphohexose isomerase* are reported to be similar to GOT in the diagnosis of MI, but less specific (West et al 1966 Coodley 1970)

Serum *gamma-glutamyl transpeptidase* activity is used principally as an indicator of hepatobiliary disease (Goldbarg et al. 1963, Rutenberg et al. 1963 Konttinen et al. 1970 Konttinen et al. 1971) but elevations of this enzyme occur in sera of patients with MI, too and so late as on the fifth day after the onset of infarction, returning to normal levels about four weeks later (Agostoni et al. 1965 Hedworth—Whitty et al. 1967 Naftalin et al. 1969). The mechanism responsible for this late increase is explained to be a disturbance of the hepatic circulation after MI (Naftalin et al. 1969) or a reparative process taking place in the infarcted heart tissue (Ravens et al. 1969)

A relatively late occurrence of peak activity of another serum enzyme, *glucose-6-phosphate dehydrogenase* has been observed in patients with MI (Kerppola et al. 1960). This enzyme test has aroused interest in connection with certain haematologic disorders.

In consequence of the deficient insight so far into these six enzyme tests in clinical use, only uncertain suppositions have been presented concerning the advantages these procedures may offer in the diagnosis of MI.

B. Enzyme tests for demonstration of liver damage after myocardial infarction

1 *Alanine aminotransferase (ALAT or GPT)*

In connection with the tests mentioned previously reference was often made to unspecific alterations of enzyme activities in the serum because of the release of these enzymes from non-cardiac sources. In addition to many unassociated conditions there are two common complications of MI capable of giving rise to problems by way of enzyme changes in suspected extension of an older MI i.e. heart failure and shock. Additional tests have been recommended for the demonstration of the participation of the liver in these enzyme alterations. Determination of alanine aminotransferase (ALAT or GPT) has been used more commonly than other enzyme tests for this purpose

Like GOT this enzyme occurs in most human tissues, and the highest activity nearly 3000 times the normal serum GPT activity has been measured in liver (Bataakis and Briere 1967 a) Markedly lower activities of GPT occur in heart and skeletal muscle and in other tissues, and the serum increase is therefore more specific for liver damage than serum GOT (Wroblewski 1959). Thus the serum GPT activity does not rise after uncomplicated MI unless there is a large necrotic area in the myocardium producing high serum GOT activities (Wroblewski and LaDue 1956 b Chinsky et al. 1957 Linde 1958 Reichard 1959 Dale and Runde 1966 Lorentz et al. 1967). MI complicated by right ventricular failure or shock may be associated with levels of GPT that are as high or higher than those of GOT (West et al. 1966). In patients with circulatory shock but without MI elevated serum GPT values have been observed in 37 per cent (Shubin and Weil 1963)

Elevated levels of serum GPT occur approximately as often as those of serum GOT in patients with an acute episode of right ventricular failure, but without MI, i.e. in 11—12 per cent of cases (Richman et al. 1961 West et al. 1961) but in patients with »pure» left ventricular failure the serum GPT activity remains normal.

2. *Lactate dehydrogenase isoenzyme LDH_5*

A high content of LDH_5, the LDH fraction with the slowest electrophoretic mobility occurs in liver but also is high in skeletal muscle and skin (Wroblewski 1963, Wieme 1964) In acute liver damages or diseases

a steep elevation of LDH_1 activity has been observed transiently in serum (Wieme and van Maercke 1961 van der Helm et al. 1962). Also in patients with MI complicated by congestive heart failure or shock the abnormalization of this fraction has been reported to be common (Goodfriend and Kaplan 1965, Aber et al. 1966, Wright et al. 1966 Lorentz et al. 1967 Coodley 1970 Auvinen and Konttinen 1971)

It is noteworthy that in normal serum little if any LDH_5 activity can be demonstrated, so that even a slight increase of this fraction — which may not alter greatly the total LDH activity — becomes clinically significant (Wieme 1964) Thus it is explicable that a change in the serum isoenzyme pattern towards slow fractions» can be detected even in chronic liver diseases although the total serum LDH remains within normal limits (Elliott and Wilkinson 1963).

Because electrophoretic fractionation of serum LDH is not feasible in most clinical laboratories, the same simplified methods have been recommended for the coarse estimation of the dominant liver pattern of LDH isoenzymes as were referred to in previous sections of this chapter

3. *Ornithine carbamoyl transferase (OCT)*

Ornithine carbamoyl transferase is involved in the synthesis of urea This enzyme is present almost exclusively in the liver (Reichard 1960 1962) The activity in the small intestine corresponds to about 14 per cent of the OCT activity in liver and other organs have only minimal activities In consequence of the liver specificity of OCT it has been used chiefly in the diagnosis of hepatocellular diseases (Moretti et al 1959 Geffroy et al 1962, Leluan 1965 Hellstrom 1966 Konttinen 1968 Konttinen et al 1970) Quite few studies have been published concerning the use of this enzyme test as an indicator of liver cell affection in patients with MI (Strandjord 1964 Dale and Runde 1966 Lorentz et al. 1967 Auvinen and Konttinen 1971). Elevated serum OCT values have been measured regularly in patients with circulatory shock (Reichard 1962). In patients with acute enteritis the abnormal OCT levels in serum may be caused by leakage from the gastrointestinal tract, but the findings of abnormal OCT activity in sera of some patients with rheumatoid arthritis and systemic lupus erythematosus are more difficult to explain (Batsakis and Briere 1967 c).

According to the opinion of most of the authors mentioned the OCT test is one of the most useful means to demonstrate minor lever damages for which other tests are not sensitive enough.

4 *Other enzyme tests as possible indicators of liver damage after myoca dial infarction*

Alkaline phosphatase was the first enzyme utilized in the examination of patients with hepatic disease (Roberts 1933) and it is still widely used in the differentiation of obstructive and hepatocellular jaundice and in the diagnosis of some bone diseases and space occupying lesions of the liver It has been tested also as an indicator of hepatic damage in patients with congestive heart failure (West et al. 1961), and abnormal values of this enzyme in serum were found in 65 per cent of 1 4 patients with an acute episode of cardiac decompensation but without acute myocardial infarction. Little is known about the effect of myocardial damage on the serum activity of this enzyme.

Isocitric dehydrogenase occurs in liver heart, skeletal muscle and red cells (Pojen et al. 1963) It has been separated into two isoenzymes, one of which occurs primarily in the liver and the other in the heart. Normal serum isocitric dehydrogenase activity is usually observed after acute MI unless there is concomitant liver cell damage (Ster

kel et al. 1958, Batsakis et al. 1964) The explanation has been offered that the unstable heart isoenzyme soon loses its activity while in the case of liver cell injury the more stable liver fraction persists (Strandjord et al. 1959)

Guanine deaminase or *guanase* is present in high concentrations in liver but comparable activities occur in kidney and brain, while low values are found in heart and skeletal muscle (Knights et al. 1965) This test has been applied to the demonstration of hepatic lesions (Coodley 1968 b Konttinen et al. 1970), but little is known about the usefulness of this test as an indicator of liver cell affection after MI.

III OBJECT OF THE PRESENT STUDY

The electrophoretic determination of LDH isoenzymes has been observed to be more accurate in the differential diagnosis of MI than the measurement of the total LDH. This procedure for LDH fractionation is, however too cumbersome and time-consuming for routine clinical use. To remedy this, simplified methods have been developed.

— The main object of the present work was the clinical evaluation of two simple tests, i.e. those for heat stable and urea stable LDH, by studying to what extent these tests are able to substitute the electrophoretic run in the differential diagnosis of patients with acute substernal pain. For comparison the electrophoretic separation of LDH isoenzymes was to be made from the same serum samples as the simple tests.

— With the object of ascertaining the position of these two tests in the enzymatic support of the mentioned differentiation, the comparative efficiencies of the routine GOT HBD and CPK tests were to be determined.

— To obtain information on the possible indicators of hepatocellular damage after MI, the value of LDH_5 isoenzyme, GPT and OCT tests were to be appraised.

— On the basis of the results of this work it was the object to choose if possible, the enzyme tests that appeared to be most suitable for routine clinical use.

IV METHODS

A. Definition of clinical concepts and diagnostic groups

Myocardial infarction (MI) as a pathologic process is necrosis of heart muscle as a complication of ischaemia, which latter may be precipitated by acute coronary occlusion or by decrease of the coronary blood supply below the vital demands of the myocardium.

Clinically MI is characterized by mostly severe and prolonged chest pain independent of physical exertion. Often one may observe signs of heart failure or circulatory shock. Other common findings are electrocardiographic changes, fever reaction, leukocytosis, and abnormal erythrocyte sedimentation rate. Serum enzyme alterations also are routine observations today

In this study the following criteria were used for the classification of myocardial infarctions

As transmural MI were defined lesions associated with a typical clinical picture of MI and the evolution of an electrocardiographic pattern, recorded by serial tracings, indicative of myocardial necrosis of penetrating extent, i.e. the appearance of QS waves with ST T-changes in at least one lead not showing this pattern without MI. Subepicardial infarctions extending beyond the electric endocardial surface (Sodi-Pallares et al. 1961) and producing a QS pattern were included in this category because they cannot be differentiated from transmural lesions except at autopsy

As non transmural MI were defined lesions associated with a clinical picture consistent with MI and the evolution of an electrocardiographic pattern, recorded by serial tracings, indicative of non-penetrating myocardial necrosis, i.e. abnormal Q waves of type QR or Qr with ST T-changes in one or more leads not showing this pattern without MI. Diagnostic criteria for inferior MI included, however ST T-changes with appearance of abnormal Q waves in leads II, III and aVF or in III and aVF The criteria for abnormality of the Q wave were a duration of 0 04 seconds or longer and a depth of 25 per cent or more of the R wave in the same complex. As non-transmural were also defined lesions producing electrocardiograms with abnormal decrease in the R waves without their disappearance as the chest electrode is moved from lead V_1 leftwards, to leads V_3 or V_4 (epicardial infarction of right lower septal mass, Sodi-Pallares et al. 1960). The evolution of abnormally tall R waves (R/S ratio equal to or greater than one) in the right chest leads also without abnormal Q waves in other leads (strictly posterior MI, Perloff 1964, Eriksen 1970) was also considered diagnostic of MI if the clinical course of the disease was consistent with MI.

Probable MI was diagnosed if the clinical picture of the disease was compatible with acute MI, the serial tracings recorded only S-T and/or T wave changes of coronary type

without any electrocardiographic evidence of myocardial necrosis (subendocardial MI) and there was leukocytosis, the white cell count being 9000 or more, or an increase of the erythrocyte sedimentation rate by 10 millimetres or more during the hospital treatment. In doubtful cases pulmonary embolism was excluded by means that will be described later

Although the presented gradation of infarcts is only a rough and approximate one it offers a possibility to arrange the patients in groups according to the extent of their myocardial damage.

Acute coronary attack without recognizable infarction (Proger and Naimi 1963) designates a grade of acute coronary heart disease less severe than acute MI In this category there were included acutely impaired conditions of clinical coronary heart disease without evidence of fresh myocardial necrosis. Such conditions were incipient or worsened angina pectoris, pre-infarction angina, acute coronary insufficiency and aggravated chest pain after MI incurred more than one month previously It is to be noted that patients with stable chronic angina pectoris, precipitated by exertion or emotion, were not included in this category

The symptoms in the patients included in this group were not distinguishable from those of patients with »slight» MI. The electrocardiograms might show signs similar to those in patients with probable MI, i.e. S-T and or T wave changes or signs of an old infarction but in some cases they might not show any changes consistent with myocardial anoxia (Lipman and Massie 1965) at the moment of investigation In addition to this there was no rise in the white cell count to 9000 nor any increase in the erythrocyte sedimentation rate to the extent mentioned under probable MI In those patients in this group who had not suffered MI or did not develop it later during the same hospitalization the diagnosis of coronary heart disease was based mainly on the typical case history the exclusion of other possible causes of the presenting symptoms, and suggestive changes in resting electrocardiograms, or in the absence of the latter changes on a positive exercise test (Lipman and Massie 1965)

It must be emphasized from the very beginning that in every unselected material of patients with coronary heart disease there are borderline cases that must be diagnosed only on the basis of secondary and unspecific criteria. In spite of little opportunity for clinicopathologic correlations in patients with coronary heart disease of slight degree it has been demonstrated that in patients with no objective signs of clinical MI and with no history of symptoms resembling it diffuse or patchy necrosis of the myocardium may be present (Snow et al. 1956 Wood 1961 Resnik 1962, Proger and Naimi 1963 Edwards 1969)

Knowing the difficulty of and the possible errors in the diagnostic grouping of these borderline cases they were not excluded from the present material since the basic purpose of this work was to examine certain means to facilitate the solution of this problem.

Heart failure is a condition in which the heart is not able to pump blood adequately in relation to the venous return and to the metabolic demands of tissues.

When *left heart failure* results in an abnormal congestion of blood in the pulmonary circulation there usually is increased transudation of fluid from the capillaries into the interstitial spaces Initially there is only interstitial oedema, detectable in chest roentgenograms but later there are audible rales.

Right heart failure is apparent from signs of elevated pressure and congestion in the systemic veins and capillaries and it may result in the development of hepatomegaly or of peripheral oedema.

The following bedside signs caused by congestive heart failure of *left ventricular origin* were considered in this work dyspnoea at

rest, tachypnoea, orthopnoea, wheezing without pulmonary disease, basal rales audible after some forced respiratory excursions, or moist rales over the entire lung fields with other phenomena of pulmonary oedema, prolonged sinus tachycardia of 110 beats or more per minute, and ventricular gallop rhythm.

The following bedside signs of *right ventricular failure* were considered in this work: observably enlarged and often tender liver peripheral ankle or sacral oedema without a local cause and a rise of jugular venous pressure over 5 cm above the level of the sternal angle in cases where the patient s condition permitted its careful esti mation and where it was clearly observable The central venous pressure was measured by the usual method in patients with MI taken into the coronary care unit, but elevated values of this pressure were not directly ascribed to right ventricular failure since simultaneous alterations in the cir culating blood volume may contribute to the central venous pressure, especially in pa tients on infusion therapy

A high incidence of congestive heart failure especially of left ventricular origin, has been observed during the acute stage of MI (Logue et al. 1963 Heikkilä 1967 Heik kilä et al. 1971) Right ventricular failure in patients with acute MI is almost regularly a result of left ventricular failure (Logue and Hurst 1966)

Pulmonary embolism is the impaction in the pulmonary vascular bed of embolic material originating mainly in thrombi of the veins of the lower extremities or the pelvis or sometimes of the right heart chambers. It has been assumed that pulmonary embolism only exceptionally is complicated by pulmonary infarction, i.e. necrosis of lung parenchyma resulting from inter ference with the blood supply (Dexter 1966). Only when the embolization occurs in medium sized arteries and in addition the bronchial collateral circulation is interfered with by pulmonary congestion or systemic hypotension does pulmonary infarction result.

In this work the diagnosis of pulmonary embolism was based on the suggestive clinical picture positive radioactive lung scanning and, in certain cases, pulmonary angiographic evidence, or characteristic ra diologic findings of pulmonary infarction. In confirming the clinical impression of pul monary embolism the electrocardiographic changes were of assistance in many cases (Lipman and Massie 1965)

In patients with massive pulmonary embolism followed by lowered cardiac output and aortic pressure there may occur crushing substernal pain indistinguishable from that caused by MI (Dexter 1966) Recognizing the numerous other difficulties in the diagnosis of pulmonary embolism, also when using the newer methods, i.e. pulmonary angiography and radioactive lung scanning only cases confirmed as far as possible were accepted for this study

Shock is defined as a condition char acterized by the insufficiency of the circula tion to bring oxidized blood to tissues and to relieve them of noxious products of metabolism. In this work shock was always a complication of MI and thus was caused primarily by the impaired pump effect of the heart. Although the mechanism of development of shock includes details inadequately explained, the clinical picture is known a low or unobtainable arterial pressure measured by conventional means, a feeble and often rapid pulse, pale, cool and moist skin and other signs of poor organ perfusion, as scanty urinary output and blunted level of consciousness. Patients with the mild stage of cardiogenic shock, synony mous with transient hypotension, were not included in the shock subgroup which com prised only patients with a fully developed picture of peripheral circulatory failure.

B. Clinical examination of patients

The patients included in the present material, to be described in detail in the following chapter were examined by the author on the same days as the blood samples were taken for enzyme analysis. At first a history of earlier cardiovascular diseases was taken and the time of onset of the present symptoms was questioned. The bedside examination was performed to detect the clinical manifestations of the condition in order to ascertain the proper diagnosis. For example, paradoxical cardiac pulsation, a pericardial friction rub and atrial or ventricular gallops may give diagnostic support in patients with suspected MI, as does a pleural friction rub or signs of deep venous thrombosis in the leg in patients with suspected pulmonary embolism. In patients with proved MI repeated examinations were performed to detect symptoms and signs of congestive heart failure and to observe the state of peripheral circulation.

Conventional 12 lead electrocardiograms were taken and the white cell count and erythrocyte sedimentation rate were determined daily during the first four days after admission and thereafter once weekly Routine chest roentgenograms in posteroanterior and lateral projections were taken of all patients with MI after their mobilization, i.e. 2—3 weeks after admission, and of patients in the other groups on one of the first few days after admission, according to the state of the disease

Of the patients with MI admitted to the coronary care unit anteroposterior chest roentgenograms were taken daily their heart function was monitored electrically and the central venous pressure was constantly measured during their stay in that unit.

C. Methods of enzyme determination

The following methods were used in this work for the measurement of serum enzyme activity

1 *Serum LDH activity* was determined by a spectrophotometric method (Wroblewski and LaDue 1955) modified by Lindy and Konttinen (1967 b) using the forward reaction from pyruvate to lactate with reduced nicotinamide-adenine dinucleotide (NADH) as coenzyme

The mean serum LDH activity in the control group used in this work (n = 35) was 153 ± 22 U l The upper normal limit with 95 per cent confidence (mean + 2 SD) was 197 U l

2. *Serum u ea stabl LDH* activity (U LDH) was measured by a procedure presented by Lindv and Konttinen (1967 b) in 2 0 M urea solution

The mean serum U LDH activity n the control group (n = 35) was 10? ± 18 U l The upper normal limit (mean + 2 SD) was 138 U/l. The mean U LDH percentage of the total LDH in this group was 66.94 ± 6 78 and the calculated normal limits (mean ± 2 SD) 53 4—80.5

3. *Serum heat stable LDH* activity (H LDH) was measured by a method presented by Strandjord and Clayson (1961) after the incubation of buffered serum at 65 C for 30 minutes. For calculation of the percentage of H LDH the total LDH activity was measured also under the same conditions as the H LDH activity but omitting the incubation.

The mean serum H LDH activity in the control group (n = 35) was 43 ± 12 U/L The upper normal limit (mean + 2SD) was 67 U/L The mean H LDH percentage of the respective total LDH in this group was 23 94 ± 6 05 and the calculated normal limits (mean ± 2 SD) 11 6—36.0

4. *Serum HBD activity* was determined by a spectrophotometric method (Elliot and Wilkinson 1961) In this procedure the reaction and the coenzyme are similar to those used in the method for the measurement of total LDH activity except that the substrate is alpha-oxobutyrate.

The mean serum HBD activity in the control group (n = 35) was 100 ± 13 U/l. The upper normal limit (mean + 2SD) was 126 U/l.

5 The separation of *serum LDH isoenzymes* was done by agar gel electrophoresis (Wieme 1959 1965) on microscope slides The electrophoretic run was carried out with LKB electrophoresis equipment at room temperature during 50 minutes at 250 V with 7,5 microlitres of serum. If the total LDH activity in serum was higher than three times the upper normal limit, only 5 microlitres was used.

The isoenzyme bands were stained as described by van der Helm (1962) but p-iodonitro-tetrazolium violet was used instead of nitro blue tetrazolium.

The isoenzymes were quantitated by scanning the stained and dried slides in a Beckman Analytrol Microzone Scanning Apparatus. The activity of each isoenzyme in U/l was calculated from the scanned distribution and the total LDH activity in the same serum.

The mean and ranges of the percentages and the absolute values of the isoenzymes (mean ± 2 SD) in the control group (n = 35) are given in Table 1

6 *Serum GOT activity* was determined by a spectrophotometric method at 30 C (Karmen et al. 1955).

The mean serum GOT activity in the control group (n = 35) was 11 6 ± 2.7 U/l and the upper normal limit (mean + 2 SD) was 17 0 U/l.

7 *Serum CPK activity* was determined by a spectrophotometric procedure based on the method presented by Tanzer and Gilvarg (1959). The modification presented in Sigma Technical Bulletin No. 40-UV (1967) and used in this work employs glutathione as a stimulating agent.

The mean serum CPK activity in the control group (n = 30) was 3 4 ± 1 7 Sigma units per ml (defined in the bulletin) and the upper normal limit (mean + 2 SD) was 6.8 Sigma units per ml.

8 *Serum GPT activity* was measured by a spectrophotometric method at 30 C (Wroblewski and LaDue 1956 b)

The mean serum GPT activity in the control group (n = 35) was 11 4 ± 5.2 U/l and the upper normal limit (mean + 2 SD) 21.8 U/l.

9 *Serum OCT activity* was measured by a colorimetric method presented by Konttinen (1968)

The mean serum OCT activity in the control group (n = 35) was 11 4 ± 5.2 U/l and the upper normal limit (mean + 2 SD) 0 48 U/l.

The determinations of serum HBD GOT and GPT activities were performed as routine analyses in the Central Laboratory of

Table 1. Serum LDH isoenzymes Normal values (n = 35) in percentages and enzym units (U/l) Range: mean ± 2 SD

	LDH isoenzyme				
	1	2	3	4	5
Mean, per cent	45 2	40.6	11.8	1.1	1.3
Range,	32 4—58 0	32.2—49 0	1.3—22.4	0—3.8	0—4.1
Mean, units	69	63	18	2	2
Upper limit, units	99	85	36	5	6

3

the hospital, and the other measurements were done or supervised by the author

The enzyme activities will be henceforth in this study expressed not in enzyme units but in relative values i.e in multiples of the upper normal limit of the enzyme activity which is designated as 1 For instance, a result presented as the multiple 3 6 means that this result was 3 6 times as high as the upper normal limit of the enzyme activity in question. By using the relative values it is possible to avoid the various enzyme units for which a uniform international practice has not yet been established. In addition, comparison of the results given by the various enzyme or isoenzyme tests is made clearer by means of the more commensurable relative values.

Standard statistical techniques have been used in this work for calculations, which were performed at the Computing Centre University of Helsinki.

V MATERIAL

The clinical examinations and the serum enzyme determinations of the patients included in this material were performed between October 1968 and March 1970 The patients were admitted during this period to the First Medical Department of the University of Helsinki with an obvious or suspected acute myocardial infarction. Most of the patients were from this city or the surrounding countryside and arrived within some hours to two days after the onset of symptoms.

All the patients with obvious or suspected MI admitted to the hospital during the stated period were included in this material, excluding, however some shorter periods of two to ten days, when collection of the material was discontinued owing to performance of accumulated laboratory work, such as scanning of electrophoresis slides.

Even if there was no conscious selection of patients for the series studied, it must be emphasized that like all clinical materials composed mostly of patients with coronary heart disease this material was in a certain sense selected. It included only those patients who had symptoms severe enough to bring them to hospital and those who had not died suddenly or at all events before admittance to hospital. In addition, excluded from this material were the patients who died within twenty four hours after their arrival, as well as patients with an estimated onset of acute symptoms of more than forty eight hours before admittance i.e. before the possibility of examination by the author

Some other not specified factors may have influenced the composition of this material. Patients with uncharacteristic symptoms and especially those with slight or no electrocardiographic signs may have been sent back from the emergency out patient department. In the absence of empty beds many patients with an urgent need of close observation in the ward were not hospitalized.

Various factors thus resulted in some kind of selection before the patients were admitted to the clinic in question. Thereafter the author determined, according to the criteria stated in the preceding chapter the diagnostic group of each patient, independent of the opinion of the physician in attendance

The total number of patients with obvious or suspected MI admitted to the clinic during the stated period and included in the present series was 176 As shown in Fig 1 these patients were placed in the following groups on the clinical grounds defined in the preceding chapter

Group 1 58 patients with transmural MI

Group 2 35 patients with non transmural MI

Group 3 9 patients with probable MI

Group 4 45 patients with acute coronary attack without recognizable acute MI and without subjective evidence of MI during the last thirty days

Group 5 14 patients with acute pulmonary embolism and without evidence of MI within the last thirty days

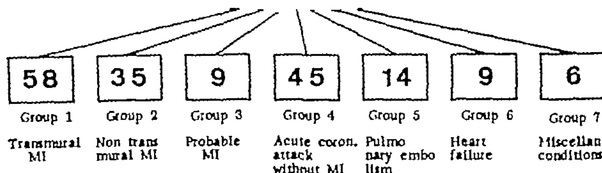


Fig. 1 Clinical diagnosis of patients admitted to hospital with obvious or suspected myocardial infarction (MI).

Group 6 9 patients with congestive heart failure without evidence of MI within the last thirty days

Group 7 6 patients with various condi tions simulating MI.

In 51 patients the main localization of MI was the anterior wall and likewise in 51 patients the posterior wall. However only 2 patients had electrocardiographic signs of a strictly posterior MI mentioned previously

The distribution of patients with MI according to sex and age is presented in Fig 2 where the patients who died in hospital (totally 21) are also shown. In 13 of these cases an autopsy was done and MI was verified in all cases.

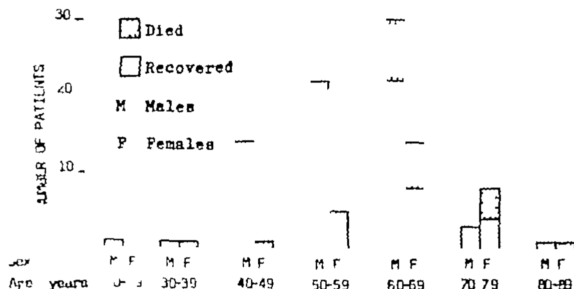


Fig 2 Distribution according to age nd se of patients with myocardial infarction Number of patients who died corresponds to the shaded part of the columns

Four of the 14 patients diagnosed to have pulmonary embolism had had acute MI more than one month before the present hospi talization, and seven had clinical signs of venous thrombosis in the leg, verified in two cases by venography The diagnosis of pulmonary embolism was based on the clinical picture compatible with this condi tion in all 14 cases, on a positive finding in radioactive lung scanning in 12 cases, and on chest roentgenograms with changes indicative of pulmonary infarction in five cases, including the two cases in which lung scanning was not done In ten cases the electrocardiographic changes (Lipman and Massie 1965) supported to some extent the diagnosis, and in one case the diagnosis was confirmed by pulmonary angiography Only one patient with pulmonary infarction died the diagnosis was verified at autopsy

All the nine patients diagnosed to have congestive heart failure had clinical signs of heart failure of both ventricles. There was no evidence of acute MI clinically or by electrocardiography in these patients of whom four had had MI more than one month before this hospitalization. In all these patients the chest roentgenogram indicated marked cardiac dilatation and signs of pulmonary congestion.

Table 2 shows the age and sex distribution of the patients in groups 1—3 and 4, 5 and 6

For calculation of the normal values of serum enzyme activities stated in the preceding chapter and used only in the present work the sera of 35 healthy factory workers were analyzed. Sick persons were excluded as far as possible by questioning and on the basis of the health cards of the factory's dispen sary For the calculation of the normal values of serum CPK activity the sera of another group were analyzed, i.e. 30 healthy members of the hospital personnel. The age and sex distributions of these two control groups are presented in Table 3.

It was the author's endeavour to examine all the patients in the present study on each of the first four days. On the first day (the first 24-hour period following the onset of acute symptoms), however it was possible to examine only half of the patients because of delayed arrival at hospital of the rest of the patients.

In addition, 37 patients with MI (included in groups 1—3 of 102 patients with MI) were examined also on the fifth, eighth, eleventh

T bl 2 *Sex and age distribution f patient*

Diagnosis	No. f patients	Age, years Mean	Sex		Age, years Range	Age, years Mean
Myocardial infarction (MI)	102	59 8	M	72	28—80	57 5
			F	30	39—89	65 2
Acute coronary ttack without MI	45	57 4	M	35	34—73	55 8
			F	10	47—79	63.1
Pulmonary embolism	14	56.7	M	9	39—74	54 6
			F	5	34—72	60 6
Heart failure	9	76.2	M	3	76—77	76.3
			F	6	68—86	76.2

Table 3 Sex and age distribution of healthy controls

	No. of persons	Age years Mean	Sex		Age, years Range	Age, years Mean
Main control group	35	47.6	M	16	37—58	44.7
			F	19	37—64	49.9
Control group for serum CPK	30	35.6	M	12	25—39	30.0
			F	18	25—65	30.4

and fifteenth days after the onset of infarction. These patients who were observed for this longer time had an obvious infarction (groups 1 and 2), whereas some of the patients in group 3 (probable MI) were discharged from hospital too early to allow this longer observation period.

The serum enzyme determinations were carried out on the same days as the clinical examinations were made with the exception of the CPK determinations, which were performed on the first four days only

Outside the original material 28 patients with certain hepatobiliary diseases were studied in order to obtain additional information on the specificity of the H LDH and U-LDH tests as compared with that of electrophoretic LDH fractionation. In the case of 23 patients with inoculation or infective hepatitis the diagnosis was based on the case history and serum bilirubin, alkaline phosphatase and transaminase measurements and additionally on liver biopsy in some cases. In all the 5 cases of obstructive jaundice the clinical diagnosis was confirmed at operation, which revealed biliary calculi in 4 cases and cancer of the pancreas in one case.

VI RESULTS

A. Enzyme tests for confirmation of myocardial infarction

1 *Sensitivity duration of abnormal activity and clinical pathologic correlation of tests*

Total LDH

The mean degree of abnormalization of serum LDH activity the standard deviation, and the number of serum samples studied on different days after MI are presented in Table 4. The first 24-hour period after the onset of acute symptoms is termed day 1 The figures designating the daily means indicate how many times these means are equivalent to (i.e. multiples of) the upper normal limit of activity of the respective enzyme

In Fig 3 is presented the scattergram of the relative values of serum LDH activity after MI. It is seen that on the first four days the values of three to nine patients were within the normal area. There were four patients whose LDH did not exceed the upper normal limit on any of these days. These four patients belonged to the Probable MI group.

The relative LDH values in the different grades of coronary heart disease are presented in Fig 4 Only the results obtained on the second and third days are shown here. On these days, which are the most conclusive for a diagnosis of MI, there also occured the peak degree of abnormalization of activity of this enzyme, as of most other enzymes. Only one to two results in the mildest group of coronary heart disease in this work were slightly above the upper normal limit. The means of each group were lower on the third than on the second day

Table 4 Mean multiple of the upper normal limit and standard deviation for serum total LDH activity in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days

	Days							
	1	2	3	4	5	8	11	15
Mean	2.6	4.1	3.6	3.1	2.6	1.9	1.3	1.0
SD	1.8	2.7	2.5	2.3	1.4	1.0	0.5	0.3
Number of samples	42	101	97	88	27	37	33	34
Percentage normal	7	6	9	7	0	19	30	71

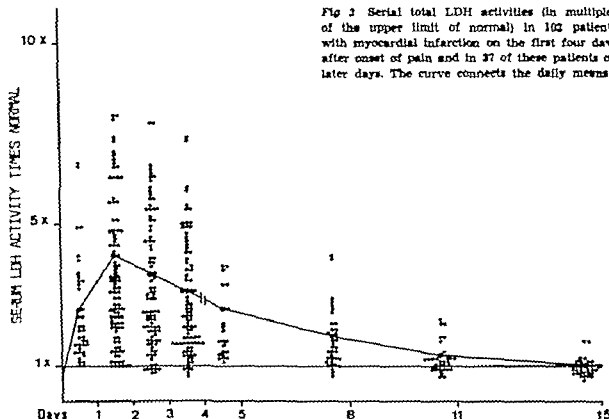


Fig 3 Serial total LDH activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days. The curve connects the daily means

LDH_1 isoenzyme determined by electrophoresis

The sensitivity of LDH_1 as percentage of total LDH in reflecting changes caused by MI is illustrated in Fig 5 Only every tenth result exceeded the upper normal limit and the mean percentage remained within the normal range during the observation time When serum LDH_1 activity was calculated in U l, there was a distinct abnormalization of LDH_1 values after MI, as is seen in Fig 6 On the first four days three to six patients had normal values and there were three patients whose LDH_1 levels did not exceed the upper normal limit on any of these days. These three patients belonged to the Probable MI group The mean degree of of abnormalization and standard deviation are presented for serum LDH_1 activity after MI in Table 5

T bl 5 Mea mult pl f th upper normal limit nd standard deviation for serum LDH_1 isoenzyme ct vity in 10 patient with myocardial inf rction on th f rst fou days after onset f pai and in 37 f these patient on later d ys

	Days							
	1	[illegible]	3	4	5	8	11	15
Mean		4 1	3 8	3 1	4	1 9	1.3	1.0
SD	1 6	5	4	3 1	1 1	1 0	0 5	0.3
Number of samples	43	10?	100	81	?7	37	33	34
Percentage normal		9	3	7	4	14	30	88

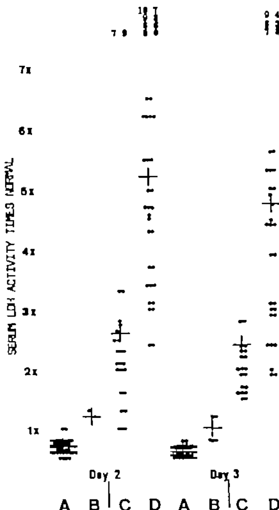


Fig. 4. Serum total LDH activities (in multiples of the upper limit of normal) on the second and third days after onset of pain, in different grades of coronary heart disease. A = acute coronary ttack without acut myocardial infarction (MI), B = probable MI, C = non-transmural MI, D = transmural *MI*. Means are marked with cross

F g. 5. Mean LDH_1 percentage ($\pm$ 2 SD) of total LDH in 102 patients with myocardial infarction on the first four days after onset f pain and in 37 of these patients on later days. The curve connects the daily means. Normal area is shaded

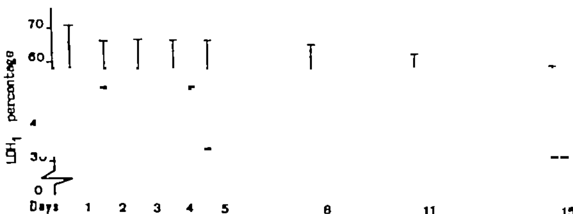


Fig. 6. Serial LDH$_1$ activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days. The curve connects the daily means.

Fig 7 Serum LDH$_1$ activities (in multiples of the upper limit of normal) on the second and third days after onset of pain, in different grades of coronary heart disease. A = acute coronary attack without acute myocardial infarction (MI), B = probable MI, C = non transmural MI, D = transmural MI. Means are marked with a cross.

In Fig 7 are presented the relative LDH_1 values in the different grades of coronary heart disease on the second and third days. In patients with acute coronary attack without MI (*group A*) all the results were within normal range on both days.

HBD

The abnormalization degree of serum HBD activity on the stated days after MI is seen in Fig 8 One to five patients had normal HBD levels on the first four days, but every one of the patients with MI showed a pathologic HBD activity on at least one of these days. The mean abnormalization degree and standard deviation of serum HBD activity after MI are presented in Table 6

Figure 9 shows the relative HBD values obtained on the second and third days, separately in the different grades of coronary heart disease. Eight of the patients with acute coronary attack without proved MI had an abnormal HBD activity on the second day (20 /) and three on the third day The highest relative value in this group was, however only 1 4 times the upper limit of normal.

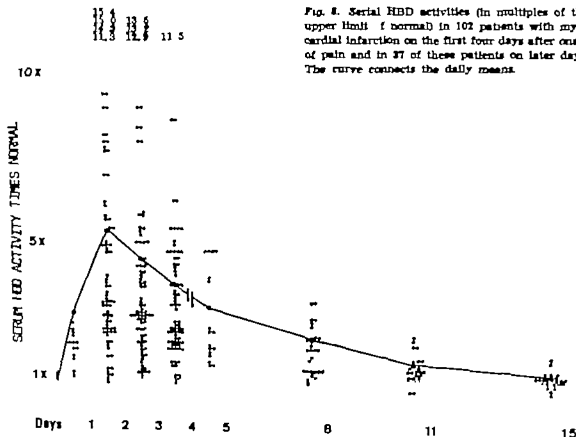
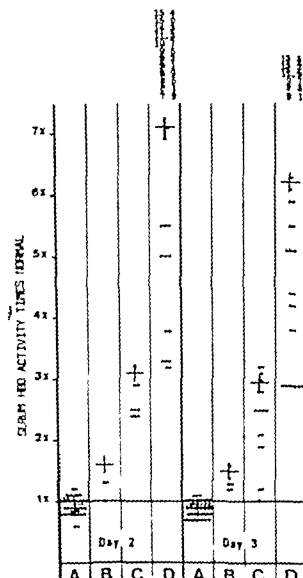


Fig. 8. Serial HBD activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days. The curve connects the daily means.

Table 6 Mean multiple of th upper normal limit and tandard deviation for serum HBD activity in 102 patiens with myocardial i f rction on the first fou days after onset of pain and in 37 of thes patients on later days

	Days							
	1	2	3	4	5	8	11	15
Mean	3.0	5.5	4 6	3.8	3.1	2.2	1.5	1.2
SD	1.9	4.1	3 5	3 1	1.6	1.2	0.8	0.5
Number of samples	23	102	90	85	25	35	31	31
Percentage normal	13		1	6	0	11	26	42



F g 9 Serum HBD activities (in multiples of the upper limit of normal) on the second and third days after onset of pain, in different grades of coronary heart disease. A = acute coronary attack without acute myocardial infarction (MI) B = probable MI, C = non transmural MI D = tran mural MI. Means re ma ked with cross.

H LDH

The individual multiple values showing the degree of abnormalization of the serum H LDH activity after MI are seen in Fig 10 Two patients were found, whose H LDH level did not exceed the upper normal limit on any of the first four days. The mean abnormalization degree and standard devia tion of the serum H LDH activities after MI are seen in Table 7

The alterations in the percentage of heat stable fraction in total LDH after MI are illustrated in Fig 11 where the daily ranges with 95 per cent confidence limits (mean ± 2SD) are also shown.

Fig 12 presents the relative H LDH values obtained on the second and third days in the different grades of coronary heart disease. In group A two patients had slightly abnormal values on both days. Because of their wide range the results of patients with transmural MI (group D) are presented only by segment of a vertical line.

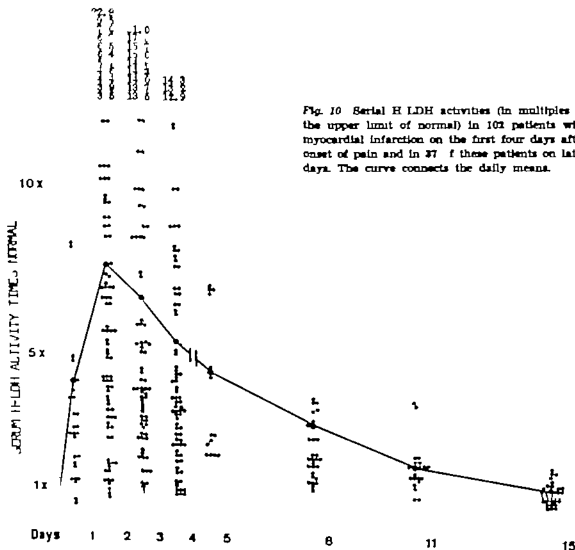


Fig 10 Serial H LDH activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 f these patients on later days. The curve connects the daily means.

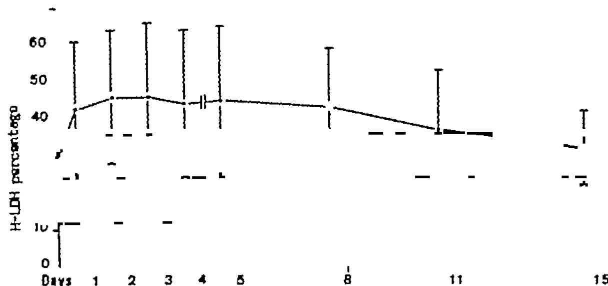
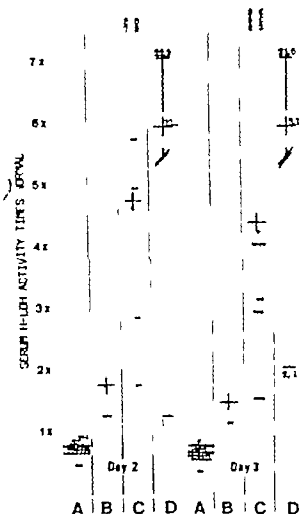


Fig. 11 Mean H LDH percentage (± 2 SD) of total LDH in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days. The curve connects the daily means. Normal area is shaded.



To obtain an idea of the correlation between H LDH and electrophoretically determined LDH_1 isoenzyme the results of these two measurements in patients with MI are plotted in Fig 13. The LDH_1 activity was calculated from the total LDH determined by the method used in the measurement of H LDH activity Generally H LDH and LDH_1 activities had a ratio of 1 1 but in low activities barely exceeding the upper normal limit the activity of LDH_1 isoenzyme was greater than that of H LDH. The situation was the same concerning the normal values of these activities. The coefficient of correlation on both the second and the third day after MI was calculated to be 0.96.

Fig. 12 Serum H LDH activities (in multiples of the upper limit of normal) on the second and third days after onset of pain, in different grades of coronary heart disease A = acute coronary ttack without acut myocardial infarction (MI), B = probabl MI, C = non transmural MI, D = transmural MI. Means are marked with a cross The range of group D is shown by segments of a vertical line

T ble 7 Mean multiple of th upper normal limit and standard deviation for serum H LDH activity in 102 patients with myocardial infarction on the first four days after onset f pain and in 37 f these patients on later days

	Days							
	1	2	3	4	5	6	11	15
Mean	4.3	7.8	6.8	5.6	4 6	3 0	1.8	1.2
SD	3.2	5.7	5.2	4 6	2.7	1.8	1.0	0 5
Number f samples	42	102	100	91	27	37	33	34
Percentage normal	5	3	4	8	0	0	33	50

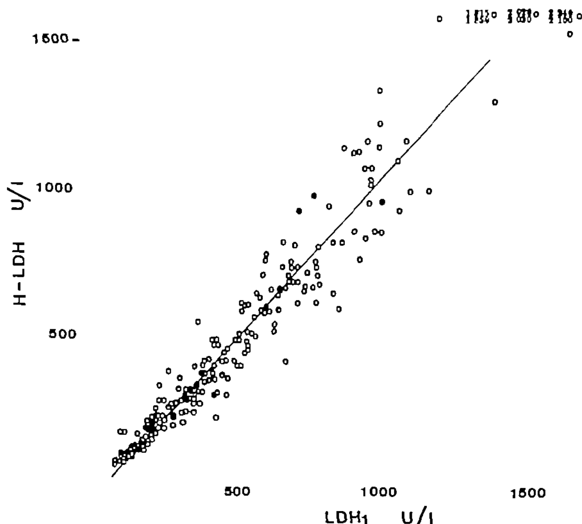


Fig. 13. Serum heat-stable LDH activities plotted against LDH_1 activities determined by electrophoresis from the same sera of 102 patients with myocardial infarction on the second and third days after onset of pain. The line is traced according to the black points which correspond to the mean H LDH and LDH_1 activities in groups Probable MI Non transmural MI and Transmural MI

U LDH

The relative values for serum U LDH activity, i.e. the abnormalization degree of individual U LDH results in patients with MI, are seen in Fig. 14. There were two patients whose results did not exceed the upper normal limit on any of the first four days after the onset of MI. The mean abnormalization degree, the standard deviation, and the daily number of samples studied on each day are presented for serum U LDH activity after MI in Table 8.

The changes occurring in the percentage of urea stable fraction in total LDH after MI appear in Fig. 15, where the daily ranges with 95 per cent confidence limits (mean ± 2 SD) are also shown. The curve connecting the daily means exceeds only slightly the

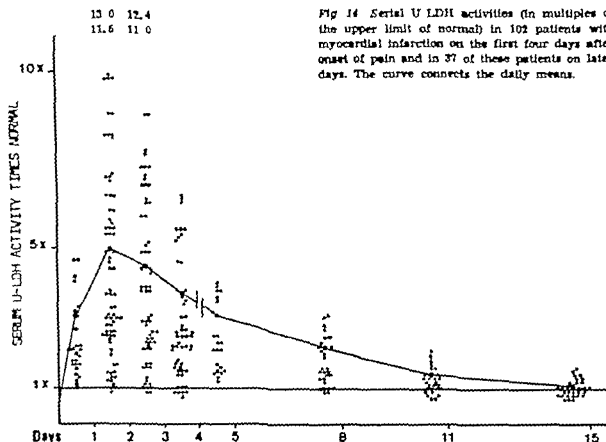


Fig. 14. Serial U LDH activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset of pain and in 37 of these patients on later days. The curve connects the daily means.

T bl 8 Mean mult ple f the upper normal limit nd st ndard deviation f serum U LDH activity 10 patients with myocardial inf rction on the f rst fou days after onset of pain and in 37 of thes patients on later day

	Day 1		3	4	5	8	11	15
Mean	3 1	5 0	4 3	3 8	2.1	[illegible]	1 4	1 1
SD	1 9	3 4	3	7	1 7	1.2	0 6	0.4
Number of samples	[illegible]	107	100	91	27	37	33	33
Percentage normal	5	3	5	9	0	16	30	67

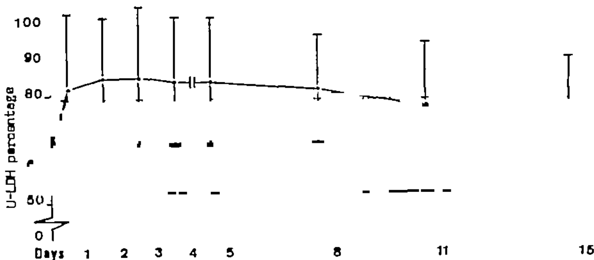
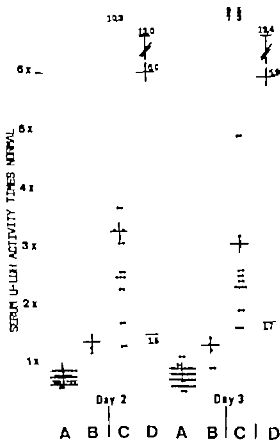


Fig. 15 Mean U LDH percentag (± 2 SD) of total LDH in 102 patients with myocardial infarction on the first four days after onset f pain and in 37 of these patients on later days. The curve connects the daily means. Normal area is shaded.

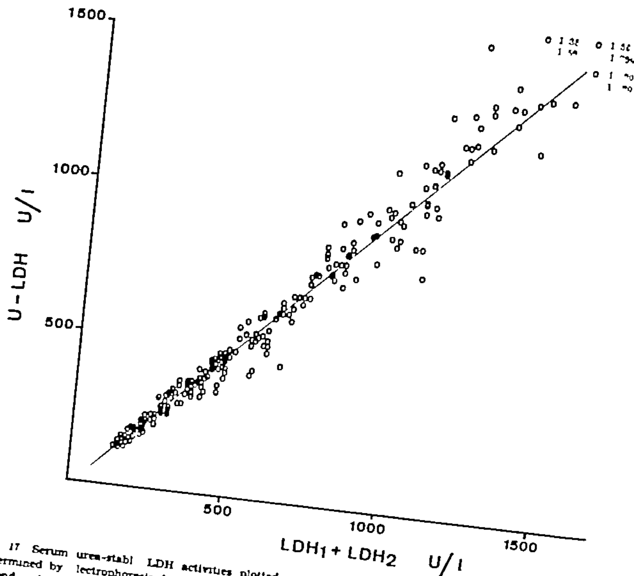


upper normal limit even on the first four days.

In Fig 16 are presented the relative U LDH values obtained on the second and third days in the different grades of coronary heart disease. In group A one to three patients had slightly abnormal values on these days. The wide range of results of patients with transmural MI is presented only by segments of a vertical line.

The coefficient of correlation between the U-LDH activity and the sum of LDH_1 and LDH_2 activities obtained by electrophoresis in patients with MI was calculated to be 0.98 on both the second and the third day after MI (Fig 17).

Fig. 16 Serum U-LDH activities (in multiples f the upper limit f normal) on the second and third days after onset of pain, in different grades of coronary heart disease. A = acute coronary attack without acute myocardial infarction (MI) B = probable MI, C = non-transmural MI, D = transmural MI. Means are marked with a cross. The range of group D is shown by segments of vertical line.



F g 17 Serum urea-stabl LDH activities plotted gainst the sum of LDH_1 and LDH_2 ctivities determined by lectrophoresis from the same sera of 102 patients with myocardial infarction on the second nd third days after onset of pain The line is traced according to the black points which cor respond t the mean U LDH and LDH + LDH_2 activities in groups Probabl MI Non trans mural MI and Transmural MI

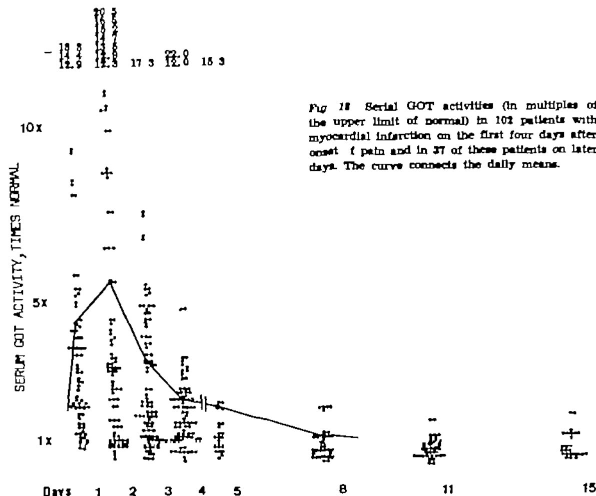


Fig 18 Serial GOT activities (in multiples of the upper limit of normal) in 102 patients with myocardial infarction on the first four days after onset f pain and in 37 of these patients on later days. The curve connects the daily means.

GOT

The degree of abnormalization of the individual GOT activities after MI is presented in Fig. 18 Especially on the second to fourth days there is an accumulation of results in the vicinity of the upper normal limit. In spite of this there were only two patients with MI whose GOT results did not exceed the upper normal limit on any of the first four days.

In Fig 19 the abnormalization of serum GOT activity is seen in the different grades of coronary heart disease on the first three days after the onset of acute pain. In group A four to seven patients had abnormal results on these days, the most abnormal values occurring on the second day The wide range in group D is presented only by segments of a vertical line.

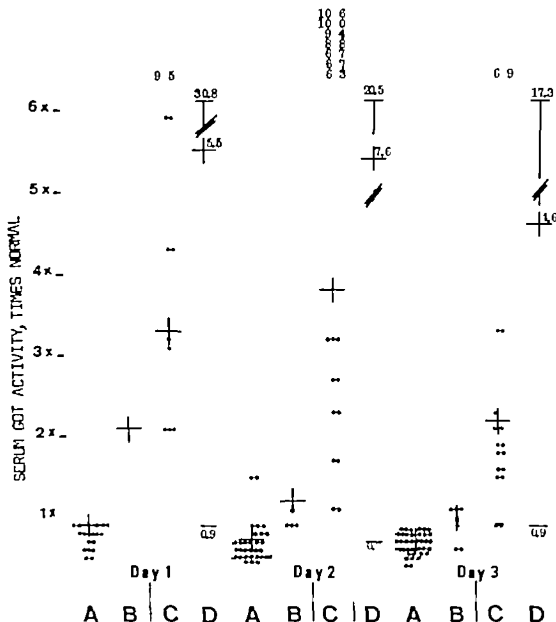


Fig 19 Serum GOT ctivities (in multiples of the upper limit of normal) on the first, second and third d ys fter onset of pain, in different grades of coronary heart disease A = acute coronary ttack w thout cute myocardial infarction (MI), B = probabl MI, C = non transmural MI, D = transmural MI Means are marked w th cross. The range of group D is shown by segments f ertical lin

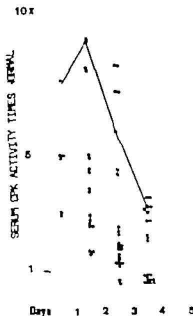


Fig. 20 Serial CPK activities (in multiples of the upper limit of normal) in 33 patients with myocardial infarction on the first four days after onset of pain. The curve connects the daily means.

CPK

The abnormalization degree of individual serum CPK activities in 33 patients with MI is seen in Fig 20 The peak values for serum CPK activity on the second to fourth days (49.0 38.5 and 18.8 times the upper normal limit) were measured in a patient with extensive transmural MI after cardiac resuscitation because of ventricular fibrillation.

Fig 21 presents the abnormalization degree of serum CPK activities in the different grades of coronary heart disease on the first three days after the onset of acute symptoms. In group A (acute coronary attack without MI 11 samples were at the most studied on any day) a total of 27 CPK determinations were performed on these days and in 19 cases (70 /) an abnormal activity was noted. In seven cases the abnormal CPK activity was not associated with an abnormal value for any other serum enzyme activity measured in this work. In the remaining 12 cases with an abnormal CPK value in group A this enzyme alteration was associated with an elevated activity of HBD (four cases), H LDH (three cases) or some other enzyme. The wide range in group D is presented only by segments of a line.

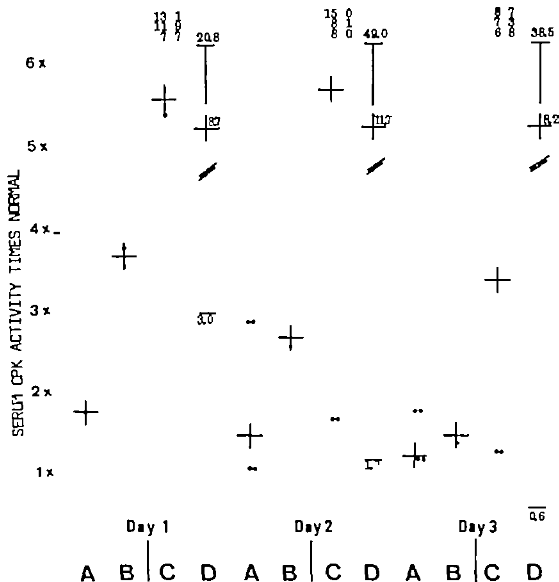


Fig. 21 Serum CPK activities (in multiples of the upper limit f normal) on the first, second and third days fter onset f pain, in different grades of coronary heart disease. A = acute coronary attack without acute myocardial infarction (MI), B = probable MI C = non-transmural MI, D = transmural MI Means are ma ked with a cross. The range of group D is shown by segments f a vertical line

2 Specificity of tests

This examination of the specificity of the enzyme tests whose other aspects were dealt with earlier in this chapter is based mainly on the results of these tests in patients with pulmonary embolism or heart failure without acute MI, in patients with miscellaneous conditions, and in patients with certain hepatobiliary diseases.

Fig 22 shows the scattergram of relative enzyme activities in patients with hepatobiliary diseases, pulmonary embolism, heart failure or acute coronary attack without recognizable MI. Fig 23 presents the remaining three enzyme activities (likewise in multiples of the upper limit of normal) in the same patients groups, but omitting patients with hepatobiliary diseases.

In the pulmonary embolism group all the enzyme tests studied very frequently showed elevated values. As many as 55 per cent of the serum LDH fractionations by electrophoresis gave a pattern similar to that obtained in patients with MI, i.e. elevated serum LDH_1 and LDH_2 activities, on the

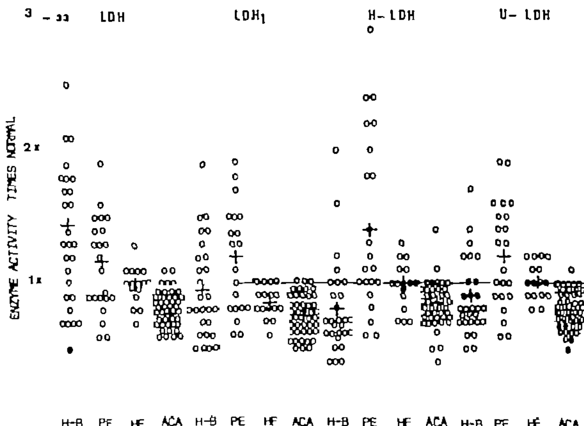


Fig 22. Serum enzyme activities (in multiples of the upper limit of normal) in 28 patients with hepatobiliary diseases (H B), in 14 patients with pulmonary embolism (PE), in 9 patients with heart failure (HF) and in 45 patients with acute coronary attack without recognizable MI (ACA). In PE and HF columns are presented the values on the second and third days, in ACA column the values on the second day after onset of acute symptoms.

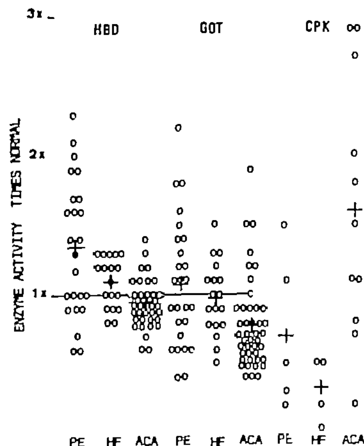


Fig. 23 Serum enzyme activities (1 multiples of the upper limit of normal) in 14 patients with pul monary embolism (PE) in 9 patients with heart failure (HF) and in 45 patients with acute coronary ttack without MI (ACA). In PE and HF columns are presented the values on the second and third days, in ACA column the values on the second day after onset of acute symptoms.

second and third days. The pattern included, it is true a concomitant elevation of LDH_3 activity in 2 cases and of LDH_3 in 4 cases. Thus no typical pattern of LDH isoenzymes was obtained in patients with pulmonary embolism. Out of eight patients with pulmonary embolism and elevated activities of serum total LDH, only three had H LDH and U LDH values or percentages that facilitated differentiation from MI

In the nine patients with heart failure slight abnormalizations were observed in most of the enzyme activities studied None of the 16 serum LDH fractionations by electrophoresis in these cases on the second and third days resulted, however in a MI like pattern, although in five of those ser the total LDH activity was abnormal. Four of these five sera showed H LDH and U LDH values or percentages that facilitated dif ferentiation from MI. Table 9 presents a summary of the enzyme activity results in the pulmonary embolism and heart failure groups.

In the group Miscellaneous conditions there were two patients with acute supra ventricular tachycardia without recognizable MI Normal results of serum LDH_1 U LDH and H LDH activities were obtained in all determinations, while slight elevations oc curred in serum total LDH and GOT values (two out of four determinations) and in serum HBD values (all three determinations) No abnormal serum enzyme elevations were

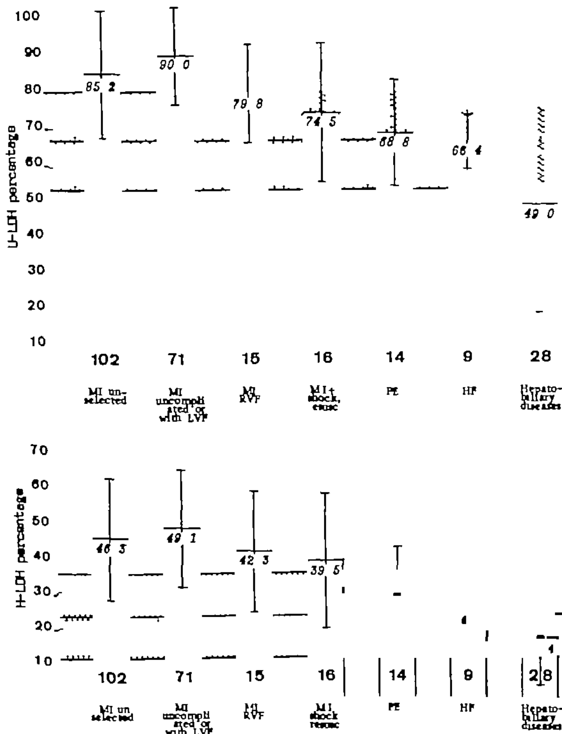


Fig 24. Mean U LDH and H LDH percentages (± 2 SD) in 102 patients with myocardial infarction (MI) on the second day after onset of pain, in 71 patients with uncomplicated MI or with MI and left ventricular failure (LVF) (based on the highest percentage on the first four days), in 15 patients with MI and right ventricular failure (RVF), in 16 patients with MI and shock or after resuscitation, in 14 patients with pulmonary embolism (PE), in 9 patients with heart failure (HF) (last, four groups based on the lowest percentage on the first four days) and in 28 patients with hepatobiliary diseases. Normal area is shaded

found in a patient with a slight (viral?) pericarditis and in another patient with thoracic pain interpreted to be of musculoskeletal origin. All the tests gave highly abnormal results in two patients with extensive tissue destruction caused in one case by cardiac resuscitation because of ventricular fibrillation not associated with acute MI, and in the other case by thrombosis of the abdominal aorta.

Table 10 is a summary of certain enzyme activity results of 28 patients with hepatobiliary diseases. Fractionation of serum LDH by electrophoresis resulted regularly in a pattern indicative of liver damage. Heat and urea inactivation eliminated in most cases the elevation of serum LDH activity of hepatic origin (Fig 22) and in the remaining cases the H LDH and U-LDH percentages were below the lower limits seen in patients with MI (Fig. 24)

T ble 9 Summary f enzyme activity results on the second and third days after onset of acute symptoms in 14 patient with pulmonary embolism and 9 patients with heart failu e not associated with acute myocardial i f rction

		LDH	LDH_1	H LDH	U LDH	HBD	GOT	CPK
Pulmonary embolism	No. of determinat.	22	20	22	22	24	25	5
	Percentage bnormal	65	55	89	65	68	48	40
Heart failure	No. f determinat.	16	16	16	16	18	18	4
	Percentage normal	31	0	31	38	56	38	0

T bl 10 Summary of enzyme activity results in 8 patients with hepatobiliary diseases

		LDH	LDH_1	H LDH	U LDH	LDH_5
Virus hepatitis	No. of determinations	23	23	23	23	23
	No. of abnormal results	15	8	3	4	22
Obstructive jaundice	No. of determinations	5	5	5	5	5
	No. of abnormal results	4	2	1	2	5

B. Enzyme tests for demonstration of liver damage after myocardial infarction

According to the definitions presented in Chapter IV clinical signs of left ventricular failure (LVF) were found in 34 patients with MI n t associated with other complications. In 15 other patients with MI the LVF was followed by right ventricular failure (RVF) but not by other complications. In 16 patients heart f ilure was associated with cardiogenic shock (4 patients) cardiac resuscitation (11 patients) r both (1 patient) Because of the small number of patients with fully developed cardiogenic shock and surviving long enough to be included in this material the results of these five patients are presented together with those of resuscitated patients. Only the results obtained from the above patients on the second to fourth days after MI were generally numerous enough to be considered here

LDH_5 determined by electrophoresis

The mean abnormalization degree and standard deviation of serum LDH_5 activity in patients with MI and various complications are seen in Table 11. The LDH_5 activities of the patients with uncomplicated MI or with MI and LVF were within or close to the normal range. The mean abnormalization degree was moderate in patients with MI and RVF but all these patients had an abnormal serum LDH_5 activity on at least one of the first four days. In patients with cardiogenic shock and in those who were resuscitated the mean abnormalization degree was up to 10 times the upper normal limit, and every patient in also this group had an abnormal serum LDH_5 activity on at least one day.

As is seen from the standard deviations, the distribution of LDH_5 values was uneven especially in groups with complications. Every other of the total number of determinations in patients with MI resulted in a normal value while some results in the groups with complications were over 60 times the upper normal limit value. The highest LDH_5 activities were observed in those patients with shock who died (four of five patients) and in patients who died after a transiently successful resuscitation (three of eleven patients).

The abnormalization degree of serum LDH_5 activity like that of the other serum enzyme and isoenzyme activities, was relatively high in patients with MI and shock or MI and cardiac resuscitation (Fig 25). The percentage of LDH activity remaining in the sera of these patients after heat or urea inactivation did not, however, differ clearly from the percentage in the total group of patients with MI in spite of high elevations of »extracardiac» isoenzymes (Fig 24).

Two out of 4 LDH_5 determinations in patients with heart failure but without acute MI gave a slightly abnormal result and six of 34 determinations in patients with pulmonary embolism resulted likewise in a slightly elevated LDH_5 value.

OCT

The mean degree of abnormalization and the standard deviation of serum OCT activity in patients with MI and different complications is seen in Table 12. The mean abnormalization degree after MI (102—37 patients) is presented in Fig 26. Likewise in patients with MI and RVF only occasional serum OCT rises were observed, and even in shock or after resuscitation most of the determinations gave normal OCT values. The peak abnormalization was 3.5 times the upper normal limit.

Table 11. Mean multiple of the upper normal limit and standard deviation for serum LDH_5 isoenzyme activity on the second, third and fourth days after onset of pain in 71 patients with myocardial infarction (MI), with or without left ventricular failure (LVF), in patients with MI and right ventricular failure (RVF) and in 16 patients with MI and shock or after resuscitation

		Days 2	3	4
MI, with or without LVF	Mean ± SD	1.0 ± 1.0	0.8 ± 1.0	0.9 ± 0.9
	Percentage abnormal	38	28	33
MI and RVF	Mean ± SD	2.6 ± 4.7	2.1 ± 2.3	2.3 ± 2.0
	Percentage abnormal	80	47	78
MI and shock or after resuscitation	Mean ± SD	9.9 ± 10.3	6.6 ± 7.5	6.4 ± 6.4
	Percentage abnormal	93	85	83

ENZYME ACTIVITY TIMES NORMAL

11x, 10x, 5x, 1x

21.0 19.5 17.0 15.7 14.3 11.8 11.4 11.1 | 12.4 11.5 | 15.0 13.2 11.5 | 15.3 13.5 12.8 11.4 | 44.9 30.8 29.8 23.7 20.5 19.9 18.0 16.0 14.3 13.9

Tot LDH, Isoenz LDH_1, H LDH, U LDH, HBD, GOT, GPT, Isoenz LDH_5, OCT

Fig. 25 Serum enzyme activities (in multiples of the upper limit of normal) in 16 patients with myocardial infarction and shock or after cardiac resuscitation. The values of two days following the resuscitation or the beginning of shock are considered.

Table 12 Mean multiple of the upper normal limit and standard deviation for serum OCT activity in 71 patients with myocardial infarction (MI) with or without left ventricular failure (LVF), in 15 patients with MI and right ventricular failure (RVF) and in 16 patients with MI and shock or after resuscitation on the second, third and fourth days after onset of pain

		Days 2	3	4
MI, with or without LVF	Mean ± SD	0.6 ± 0.4	0.7 ± 0.4	0.8 ± 0.4
	Percentage abnormal	4	18	25
MI and RVF	Mean ± SD	0.9 ± 0.6	0.5 ± 0.5	0.6 ± 0.4
	Percentage abnormal	33	20	15
MI and shock or after resuscitation	Mean ± SD	1.2 ± 0.7	1.1 ± 1.1	0.8 ± 0.6
	Percentage abnormal	47	31	17

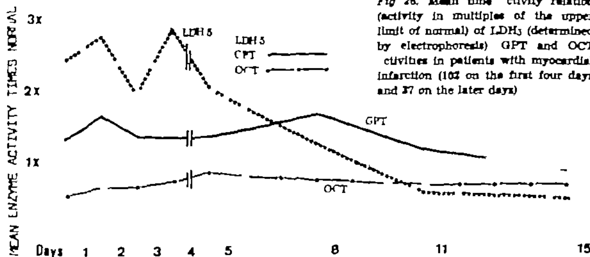


Fig 26. Mean time ctivity relation (activity in multiples of the upper limit of normal) of LDH_5 (determined by electrophoresis) GPT and OCT ctivities in patients with myocardial infarction (102 on the first four days and 37 on the later days)

Table 13 Mean multiple f the upper normal limit and standard deviation for serum GPT activity on the second, third and fourth days after onset f pain i 71 patients with uncomplicated myocardial infarction (MI) or MI and left ventricula failure (LVF), in 15 patients with MI and right ventricula failure (RVF) and in 16 patients with MI and shock or fter resuscitation

		Days 2	3	4
MI, with or without LVF	Mean ± SD	1.2 ± 1.0	1 0 ± 0.7	1.1 ± 0.9
	Percentage abnormal	53	34	40
MI and RVF	Mean ± SD	1 5 ± 0 9	1.5 ± 0.9	1 2 ± 0.6
	Percentage abnormal	73	64	42
MI and shock or after resuscitation	Mean ± SD	2 9 ± 1 7	2.9 ± 2.3	2.3 ± 1 8
	Percentag abnormal	94	92	92

In patients with heart failure (without acute MI) four of 27 OCT determinations gave a slightly abnormal value and in patients with pulmonary embolism nine of 36 determinations gave likewise a slightly elevated result.

The serum OCT determinations in patients with hepatobiliary diseases resulted regular ly in an abnormal value, with a peak abnormalization degree nearly 10 times the upper limit of normal.

GPT

The mean abnormalization degree and standard deviation of serum GPT activity after MI accompanied by various complications are seen in Table 13. The mean abnormalization degree on different days after MI (102—37 patients) is presented in Fig 26.

The abnormal GPT values in patients with uncomplicated MI or with MI and LVF were associated with highly abnormal GOT ac tivities in the same sera. Neither in patients with MI and RVF did the rise of serum GPT activity exceed that of serum GOT activity Only in four of the resuscitated patients was a greater elevation of GPT than of GOT observed at least once.

In the patients with pulmonary embolism 10 of 41 GPT determinations (24 /) gave slightly abnormal results. In patients with heart failure without acute MI four of 28 GPT determinations likewise gave slightly abnormal results (14 /)

anticoagulants, which were not given to the patients with acute coronary attack without MI in this study

Abnormalization frequencies of serum GOT varying between 3 and 40 per cent in patients with congestive heart failure have been reported earlier (Agress 1959 Richman et al. 1961 West et al. 1966 Crowley 1968) the results presented here are in agreement with this.

With a few exceptions (LaDue et al. 1954 Wacker et al. 1961) slightly elevated GOT values have been measured in patients with pulmonary embolism or infarction in 14—50 per cent of cases (Agress 1959 Stevens and Burdette 1964, Vincent and Rapaport 1965 West et al. 1966 Sasahara et al. 1967 Coodley 1969), as also were measured in the present work.

The highest GOT abnormalizations have been observed in acute hepatocellular diseases (Zimmerman and West 1963). Slight rises have been reported to occur after strenuous exercise (Garbus et al. 1964 Swaiman and Awad 1964) Although the effect of hemolysis upon the GOT activity is only slight, this test seems not to be an equally good indicator of MI as the serum LDH test is, mainly because of its poor sensitivity and the short duration of abnormal GOT activities after a small MI.

The CPK test is recommended for the confirmation of MI principally because of its greater specificity as compared with other enzyme tests, possibly with the exception of the LDH isoenzymes (Dreyfus et al. 1960 Colombo et al. 1962, Hess and Mac Donald 1963 Schneider and Heise 1963 Smith 1964 Duma and Siegel 1965 Nissen et al. 1965 Preston et al. 1965 a, Vincent and Rapaport 1965 Warburton et al. 1965 Batsakis and Briere 1966, Schneider and Lehmann 1966 Cook 1967 Crowley 1968 Coodley 1968 a) Although the evaluation of the specificity of this test is based on a few cases, in this work, the trend mentioned can be seen Recent unpublished results obtained in our laboratory for patients with pulmonary embolism are indicative of normal CPK activities in pulmonary embolism with the exception of a few patients showing a slight rise as is reported earlier (Hess and Mac Donald 1963 Vincent and Rapaport 1965 Zundel and Tyler 1965) These results are explicable on the basis of the low CPK content of the lung (Velez-Garcia et al. 1966 *Perkoff 1968*) and the absence of it in the liver

The high CPK content in the myocardium makes it easy to understand that after MI great elevations of serum CPK activity have been measured, i.e. mean rises of even more than ten times the upper normal limit (Hess et al. 1964, Sigma Technical Bulletin 1967) with which the present results correspond well. Especially the methods using sulfhydryl compounds as activator (as glutathione in the method used in this study) have shown a fivefold sensitivity compared with unstimulated methods, as mentioned earlier in this report.

As a logical consequence of the improved sensitivity of the CPK test may be regarded that abnormal activities of this enzyme are measured in patients with small myocardial lesions as compared with possibly normal results obtained by less sensitive procedures. In this work slightly elevated CPK activities occurred commonly in patients with acute coronary attack without recognizable MI. It must be emphasized that these patients, as defined earlier did not have a stable angina but an acutely aggravated grade of coronary heart disease. In most cases the elevated CPK activity was associated with a slightly abnormal value of some other serum enzyme with good test sensitivity Elevated CPK activities in the sera of patients with coronary insufficiency have been observed in fact by other workers too (Forster and Escher 1961 Schneider and Heise 1963 Hess et al. 1964)

The difficulty in defining the upper normal limit or the discriminatory line for serum

CPK activity is known of old and is solved usually by leaving a borderline area between the upper limit of normal and the »discriminatory line» This line is adjusted to correspond to the clinically observed limit between patients without recognizable myocardial necrosis and those with MI. The last named limit is, however only an artificial one, and careful studies have shown that many »ischaemic» patients may have small fibrotic scars in the myocardium without clinical MI (Wood 1961 Resnik 1962, Proger and Naimi 1963 Edwards 1969) and may run the risk of getting a lethal arrhythmia, like patients with proved MI. The methods to detect minor myocardial damages have thus been too insensitive.

To facilitate comparison the upper limit of normal CPK values was calculated in this work in the same manner as those for the other enzyme and isoenzyme tests (mean ± 2 SD thus giving 95 per cent confidence) If the discriminatory line recommended by the manufacturer of the reagents used in this work is accepted, there are no abnormal activities in patients with acute coronary attack without proved MI, but there are numerous false negative results in patients with confirmed MI, also on the first three days.

At least the most greatly elevated CPK activities observed in »ischaemic» patients in this work may be interpreted to represent a small myocardial necrosis not detected by other means. Another explanation may be leakage of this enzyme through cell membranes with an increased permeability due to anoxia. Some experimental evidence suggesting this has been presented (Henry et al. 1970 Wexler 1970)

In view of th unspecific causes of CPK elevation mentioned earlier in this report and of the good sensitivity f activated procedures for its determination, a persistently normal serum activity of this enzyme will offer the most valuable information for the exclusion of necrosis or other damage in the myocardium, also in patients with congestive heart failure or suspected pulmonary embolism. Elevated CPK values are confirmatory of myocardial damage only if disorders or conditions known to be able to elevate the serum CPK can be excluded.

Recently a method for separation of serum CPK isoenzymes has been developed (Somer and Konttinen 1972) which is sensitive enough for clinical use The preliminary results with this method seem to give more accuracy in the diagnosis of MI (Konttinen and Somer 1972)

In all patients with MI complicated by RVF abnormal serum LDH_5 isoenzyme values were observed on at least one of the first four days after the onset of infarction. Transient LDH_5 rises have been demonstrated in corresponding cases by others (Wieme and van Maercke 1961, Aber et al. 1966 Cohen et al. 1966, Lorentz et al. 1967)

The changes in the enzyme and isoenzyme activities of the sera of patients with MI complicated by liver congestion are generally believed to be caused by an abnormal mechanical congestion of venous blood in the liver It has been demonstrated by several investigators that arterial hypoxaemia and other blood gas changes are constantly seen in patients with acute MI (Kirby and McNicol 1966 Naeverson 1966 Valentine et al. 1966, Ljungström et al. 1967 Pain et al. 1967 Valencia and Burgess 1969). Thus it may be understandable that LDH_5 and other noncardiac enzyme and isoenzyme changes can occur in some patients with MI in the absence of clinical signs of abnormal congestion, as was the case in this work.

In addition to liver cell changes, multiple organ damage was reflected by the elevation of all LDH isoenzyme activities in some patients with severe cardiogenic shock in both the present and another investigation (Batsakis and Briere 1967 a). High values of LDH_4 activity were measured in patients with MI

after cardiac resuscitation, and the highest activities in those patients who died after transiently successful resuscitation. The direct-current electroshock releases LDH_5 isoenzyme and other enzymes from skeletal muscles (Konttinen et al. 1969) and after external cardiac massage various LDH isoenzyme patterns have been obtained (Cohen et al. 1966).

Since OCT has been found to be present almost exclusively in the liver (Reichard 1960 1962) it has been regarded as the most specific and sensitive indicator of hepatocellular damage and as even more sensitive than GPT for the detection of certain secondary liver cell affections, as in congestive heart failure. Later this test has been recommended for the indication of liver cell damage in acute MI (Dale and Runde 1966 Strandjord and Clayson 1966 b Lorentz et al. 1967) and in alcoholics (Konttinen et al. 1970).

The inadequate sensitivity of the OCT method used for the demonstration of liver cell damage after acute MI was apparent in this work. The same conclusion has been presented by other workers concerning another method (Lehmann and Schneider 1966) Reproducible results could be obtained here only by using sterile or disposable test tubes for serum OCT determinations. Recently it has been suggested (Romslo 1972) that by using a bactericidal compound in the method for serum OCT determination (Konttinen 1968) the artificial production of ammonia can be prevented making thus the method more reliable.

For the indication of certain primary liver cell lesions this OCT method can be stated to be sensitive enough (Auvinen and Konttinen 1971).

Abnormalization of serum GPT activity was observed in half of the patients with acute MI in this study which is in agreement with another report (Dale and Runde 1966) These authors could not demonstrate any significant difference in the GOT/GPT ratios in patients with uncomplicated MI and in those having MI with associated liver cell affection. This ratio was not calculated in the present work. Lorentz and his co-workers (1967) reported higher incidences of abnormal GPT values soon after MI, with the explanation that these rises are caused by anoxic membrane damage in liver cells. However a considerable proportion of patients with uncomplicated MI in the present work had slightly elevated GPT values, associated with a greatly elevated GOT activity in the same sera. Thus the myocardium is another probable cause of these GPT elevations.

Higher incidences of abnormal GPT values were observed in cases of MI complicated by RVF than in those without complications, but the degree of abnormalization of GPT activity was no greater than that of GOT with the exception of a few cases with severe cardiogenic shock or after cardiac resuscitation. This disagrees with statements that GPT activities exceed those of GOT in patients with severe RVF (Chinsky et al. 1957 Reichard 1959 West et al. 1966) Thus the interpretation of elevated GPT values in patients with MI is rather indefinite and the evidence offered by similar or greater elevations of GPT than of GOT is obtained only in cases in which the participation of the liver and other organs is obvious.

VIII SUMMARY

A clinical evaluation of two simple tests for LDH isoenzyme estimation, i.e. heat and urea inactivation tests (H LDH and U LDH), was made by comparing the results with those obtained by electrophoretic fractionation of serum LDH. A comparison with the serum HBD GOT and CPK activities was included in the study. In addition, serum LDH_5 isoenzyme, GPT and OCT activities as indicators of liver damage after myocardial infarction (MI) were compared.

In a series of 176 patients admitted to hospital because of acute substernal pain a clinical study was made and the serum enzyme activity measurements were performed on the first four days after the onset of symptoms. Of these subjects 102 met the criteria for MI, and in 37 cases in this MI series the clinical and laboratory study was made also on the fifth, eighth, eleventh and fifteenth days.

Fifteen of the patients with MI developed signs of right ventricular failure, 5 went in cardiogenic shock (4 died), and 11 were resuscitated (external cardiac massage and/or electric defibrillation 3 died). A total of 21 patients in the MI series died during the hospitalization. In 13 of these cases an autopsy was done and MI was verified in all of them.

Of the remaining 74 patients 45 had an acute coronary attack without recognizable MI, in 14 cases the diagnosis was pulmonary embolism, 9 patients had congestive heart failure and 6 patients had miscellaneous diseases. The enzyme tests were also performed in 28 patients with hepatobiliary diseases and in 35 healthy control persons.

In patients with MI the U LDH test was observed to measure the sum of the LDH_1 and LDH_2 activities (correlation coefficient = 0.98) and the H LDH test the LDH_1 activity (correlation coefficient = 0.96). Thus these simplified tests gave information similar to that given by electrophoretic separation of LDH isoenzymes in the diagnosis of MI.

The best information of liver affection after MI was obtained by the electrophoretic LDH_5 determination. Serum GPT and OCT measurements offered very little assistance in this respect. In patients with MI complicated by shock or after cardiac resuscitation there was marked elevation of all enzyme activities from extracardiac sources, and the contribution of the myocardium to these alterations could not be evaluated by the tests studied.

Patients with pulmonary embolism showed no typical pattern of LDH isoenzymes, and differentiation from MI was not greatly facilitated by H LDH or U-LDH or by most of the other tests used.

In uncomplicated cases of MI the determination of total LDH is an adequate routine test for the confirmation of MI. A slightly better sensitivity and a longer duration of abnormal activity are the principal benefits offered by the measurement of serum HBD. Even more sensitive is the CPK test for the demonstration of small myocardial lesions. The serum GOT test is an unsatisfactory indicator of these small lesions and has a poor specificity.

REFERENCES

Aber C. P Brunt, P E., Jones, E. W Richards, T G Short, A. H., Bernstein, V Liver function after myocardial infarction. Lancet 1 1391, 1966.

Agostoni, A., Ideo, G Stabilini, R. Serum gamma glutamyl transpeptidase activity in myocardial infarction. Brit. Heart J 27 688, 1965

Agress, C. M. Evaluation of the transaminase test. Amer. J Cardiol. 3 74 1959.

Amador E., Potchen, E. J Serum lactic dehydrogenase activity and radioactive lung scanning in the diagnosis of pulmonary embolism. Ann. intern. Med. 65 1247 1966

Amelung, D. Enzymatic diagnosis of myocardial infarction. Dtsch. med. J 13 383, 1962.

Appella, E., Markert, C. L. Dissociation of lactate dehydrogenase into subunits with guanidine hydrochloride. Biochem. biophys. Res. Commun. 6 171 1961.

Auvinen, S., Konttinen, A. The diagnostic value of serum LDH isoenzymes and heat-stable and urea-stabl LDH measurements. Acta med. scand. 189 191, 1971

Babson, A. L. The chemical differentiation of tissue lactic dehydrogenase. Clin. chim. Acta 16 121, 1967

Barnett, H Electrophoretic separation of lactate dehydrogenase isoenzymes on cellulose acetate. Biochem J 84 83P 1962.

Barnett, H. The staining of lacti dehydrogenase isoenzymes after electrophoretic separation on cellulose-acetate. J clin. Path. 17 567 1964.

Baron, D N. Clinical enzymology with particular reference to liver disease. Proc. roy Soc. Med. 56 173 1963

Batsakis, J G Briere, R O Preston, J A. Clinical enzymology II Estimation of serum enzyme activity levels in hepatobiliary disease. Univ Mich. med Center J 30 278 1964

Batsakis, J G Briere, R. O Enzymological confirmation f myocardial infarction. Geriatrics 21 182, 1966.

Batsakis, J G Briere, R O Clinical enzymology in cardiovascular and related disorders I Interpretive Enzymology J G Batsakis and R. O Briere. Springfield, Ill. Charles C Thomas, 1967 a.

Batsakis, J G Briere, R. O Disorders of skeletal muscle. I Interpretive Enzymology J G Batsakis and R. O Briere. Springfield, Ill. Charles C Thomas, 1967 b.

Batsakis, J G Briere, R. O. Serum enzyme activity in hepatobiliary disease. *In* Interpretive Enzymology J G Batsakis and R. O Briere. Springfield, Ill. Charles C Thomas, 1967 c.

Batsakis, J G Briere, R. O Clinical enzymology and diseases of the lung. A critical reappraisal. Geriatrics 23 97 1968.

Batsakis, J G Briere, R. O LDH isoenzymes by urea inhibition and substrate (lactate) modification. clinical evaluation. Clin. Biochem. 2 171 1969

Bell, R. L. Separation of serum lactic dehydrogenase originating in myocardial and hepatic tissue, by means of heat fractionation. Amer J clin. Path. 40 216 1963

Bigazzi, P L., Ciampi, G P Nuovi tests enzimologici nella diagnostica dell'infarto miocardico. Progr Med. (Napoli) 19 590 1963.

Bohn, L., Bendixen, G Hjermind, P Hamning af serum laktatdehydrogenase-aktiviteten med urinstof ved diagnosen af hjerteinfarkt. Nord. Med. 76 1467 1966.

Bohn, L., Nissen, N I. Serum-lactate-dehydrogenase isoenzymes in myocardial and hepatic disease. Nord. Med. 77 106, 1967

Cahn, R. D Kaplan, N O Levine, L., Zwilling, E. Nature and development of lactic dehydrogenases. Science 136 962, 1962.

Chappell, J S., Perry S. V Creatine phosphokinase assay and application for the microdetermination of the adenine nucleotides. Biochem. J 57 118 1954.

Chinsky M., Wolff, R. J Sherry S. Serum transaminase activity A comparison of the pyruvic and oxalacetic transaminase. Amer J med. Sci. 233 400, 1957

Cho, A. K., Haslett, W. L., Jenden, D. J. A titrimetric method for the determination of creatine phosphokinase. Biochem. J. 75 115 1960.

Cohen, L., Djordjevich, J. Ormiste, V. Serum lactic dehydrogenase isoenzyme patterns in cardiovascular and other diseases with particular reference to acute myocardial infarction. J. Lab. clin. Med. 64 355 1964.

Cohen, L., Djordjevich, J. Jacobsen, S. The contribution of isoenzymes of serum lactic dehydrogenase (LDH) to the diagnosis of specific organ injury with special reference to myocardial injury. Med. Clin. N. Amer. 50 193, 1966.

Cohen, L., Larson, L. Activation of serum lactic dehydrogenase. New Engl. J. Med. 275 465, 1966.

Colombo, J. P. Richterich, R., Rossi, E. Serum-Kreatin-Phosphokinase- Bestimmung und diagnostische Bedeutung. Klin. Wschr. 40 37 1962.

Coodley E. L. Use of enzymes in cardiac diagnosis. Angiology 16 209 1965

Coodley E. L. Evaluation of enzyme diagnosis in myocardial infarction. Amer. J. med. Sci. 256 300, 1968 a.

Coodley E. L. Serum guanase in the diagnosis of liver disease. Amer. J. Gastroent. 50 55 1968 b.

Coodley E. L. Enzyme profiles in the evaluation of pulmonary infarction. J. Amer. med. Ass. 207 1307 1969

Coodley E. L. Diagnostic Enzymology. Philadelphia, Pennsylvania. Lea and Febiger 1970.

Cook, V. P. Serum creatine phosphokinase in myocardial damage. Amer. J. med. Technol. 33 275, 1967

Crowley L. V. Creatine phosphokinase activity in myocardial infarction, heart failure, and following various diagnostic and therapeutic procedures. Clin. Chem. 14 1187 1968.

Dale, J. Runde, I. Liver cell affection in myocardial infarction revealed by elevated serum ornithine carbamoyl transferase. Acta med. scand. 180 671, 1966.

Dawson, D. M., Fine, I. H. Creatine kinase in human tissue. Arch. Neurol. (Chic.) 16 175, 1967

Deul, D. H., van Breeman, J. F. L. Electrophoresis of creatine phosphokinase from various organs. Clin. chim. Acta 10 276, 1964.

Dexter L. Pulmonary embolism and acute cor pulmonale. I The Heart. J. W. Hurst and R. B. Logue (ed). McGraw-Hill, New York 1966.

Dietz, A. A., Lubrano, T. Separation and quantitation of lactic dehydrogenase isoenzymes by Disc Electrophoresis. Analyt. Biochem. 20 246, 1967

Dietz, A. A., Lubrano, T. Hodges, V. K. Comparison of electrophoresis and urea inhibition for the estimation of serum lactic dehydrogenase isoenzymes. Clin. Chem. 14 800 1968.

Di Giorgio, J. Determination of serum lactic dehydrogenase isoenzymes by use of the Diagnotest» cellulose acetate electrophoresis system. Clin. Chem. 17 326, 1971.

Dioguardi, N. Agostoni, A., Fiorelli, G. Lomanto, B. Characterization of lactic dehydrogenase of normal human granulocytes. J. Lab. clin. Med. 61 713, 1963.

DiSabato, G. Kaplan, N. O. Denaturation of lactic dehydrogenase. J. biol. Chem. 240 1072, 1965.

Doran, G. R., Wilkinson, J. H. Serum creatine kinase and adenylate kinase in thyroid disease. Clin. chim. Acta 35 115, 1971

Dreyfus, J. C., Schapira, G. Scebat, L., Resnais, J. Lenegre, J. Les enzymes sériques dans le diagnostic des lésions myocardiques d'origine coronarienne. II. La créatine-kinase. Arch. Mal. Coeur 2. 187 1960

Dreyfus, J. C., Schapira, G. Biochemistry of Hereditary Myopathies. Springfield, Ill. Charles C Thomas, 1962.

Dubach, U. C., von Orelli, A. Diagnostische Bedeutung der hitzestabilen Isoenzymfraktion der Laktatdehydrogenase beim Herzinfarkt. Helv. med. Acta 4/5 685 1963.

Dube, V. Hunter D. T. Knight, J. A., Automated spectrophotometric assay of serum lactic dehydrogenase and hydroxybutyrate dehydrogenase with clinical evaluation. Amer. J. clin. Path. 50 491 1968.

Duma, R. J. Siegel, A. L. Serum creatine phosphokinase in acute myocardial infarction. Arch. intern. Med. 115 443, 1965.

Ebashi, S., Toyokura, Y. Momoi, H., Sugita, H. High creatine phosphokinase activity of sera of progressive muscular dystrophy. J. Biochem. 46 103, 1959

Edwards, J. E. What is myocardial infarction? Circulation 15 IV—5 Suppl. No. 4, 1969

Elliott, B. A., Wilkinson, J. H. Serum alpha-hydroxybutyric dehydrogenase in myocardial infarction and liver disease. Lancet 1 698, 1961.

Elliott, B. A., Jepson, E. M., Wilkinson, J. H. Serum alpha-hydroxybutyrate dehydrogenase — new test with improved specificity for myocardial lesions. Clin. Sci. 23 305 1962.

Elliott, B. A., Wilkinson, J. H. The relative efficiences of some serumenzyme tests in the diagnosis of myocardial infarction. Lancet 2 71, 1962.

Elliott, B. A., Wilkinson, J. H. The serum »alpha-hydroxybutyrate dehydrogenase» in diseases

other than myocardial infarction. Clin. Sci. 24 343 1963

Emerson, P M., Wilkinson, J H. Urea and oxalate inhibition of the serum lactate de hydrogenase. J clin. Path. 18 803 1965.

Emery A. E. H., Moores, G E., Hodson, V.. The determination of lactate dehydrogenase (LDH) isoenzymes with urea. Clin. chim. Acta 19 159 1968.

Ennor A. H., Rosenberg, H.. Some properties of creatine phosphokinase. Biochem. J 57 203, 1954.

Eriksen, J ECG in strictly posterior myocardial infarction. Acta med. scand. 187 465 1970.

Forster G Escher J Di Kreatinphosphokinase in der Diagnostik von Herzinfarkt und Myopathien. Helv med. Acta 28 513, 1961.

Forster G.. Zur Enzymdiagnostik von Herzinfarkt und Myopathien. Schweiz. med. Wschr 97 329 1967

Foy R. B., King, R. W Serum lactic dehydrogenase isoenzyme assay by chemical inhibition. Enzym. biol. clin. 10 305, 1969

Freeman, L, Opher A. W Lactic dehydrogenase isoenzymes in myocardial infarction. Amer J med. Sci. 250 131, 1965

G rbus, J Highman, B Altland, P D Serum enzymes and lactic dehydrogenase isoenzymes after exercise and training in rats. Amer J Physiol. 207 467 1964

Geffroy Y Fablet, J Lelievre, L., Deshayes, P Interet d dosage de l ornithine-carbamyl transferase serique en pathologie hepatobiliaire. Rev int. Hepat 12 685, 1962

Gelb, D West, M., Zimmerman, H. J Serum enzymes in disease IX Analysis of factors respons ble for levated values in infectious mononucleosis Amer J Med. 33 249 1962.

Goble, A J O'Brien, E. N Acute myocardial ischemia Significance of plasma-transaminase activity Lancet 2 873 1958

Goldbarg, J A., Pineda E P Smith, E E Friedman, O M Rutenberg, A. M A method for the colorimetric determination of gamma glutamyl transpeptidase in human serum enzymatic activit in health and disease Gastroenterology 44 127 1963

Goldberg, E. Lactic and malic dehydrogenases in human spermatozoa Science 139 602, 1963

Goodfriend, T L., Kaplan, N O Isoenzymes in clinical diagnosis C rcul t on 32 1010 1965.

Graig, F A., Ross, G Serum creatine-phosphokinase in thyroid dise e Metabolism 12 57 1963.

Graig, F A., Smith, J C Serum eatine phosphokinase activity in thyroid tates J lin Endocr 25 723, 1965.

Graig, F A., Smith, J C. Creatine phosphokinase in thyroid Isoenzyme composition compared with other tissues. Science 156 254 1967

Griffiths, P D Serum enzymes in diseases of the thyroid gland. J clin. path. 18 660 1965

Griffiths, P D Serum levels of ATP creatine phosphotransferase (creatine kinase) the normal range and effect of muscular activity Clin. chim. Acta 13 413, 1966.

Halonen, P I., Konttinen, A. Effect of physical exercise on some enzymes in the serum. Nature 193 942, 1962.

Handa, S. P Serum lactic acid dehydrogenase isoenzyme determination in myocardial infarc tion. Postgrad. med. J 43 141 1967

Hansson, A., Johansson, B Sievers J Serum alpha-hydroxybutyric dehydrogenase in myocardial infarction and liver disease. Lancet 1 167 1962.

Hansson, A. Alpha-hydroxybutyrate dehydrogenase v.lactate dehydrogenase. Lancet 2 610 1962.

Hardy S. M. Simple determination of heart specific lactic dehydrogenase isoenzyme in serum. Nature 206 933 1965.

Hedworth-Whitty R. B Whitfield, J B Richardson, R. W Serum gammaglutamyl transpeptidase activity in myocardial ischaemia. Brit. Heart J 29 432, 1967

Heikkilä, J Mitral incompetence as a complication of acute myocardial infarction. Acta med. scand. Suppl. 475 1967

Heikkilä, J Luomanmäki, K., Pyörälä, K. Serial observations on left ventricular dysfunction in acute myocardial infarction. I. Gallop sounds, ventricular asynergy and radiological signs. Acta med. scand. 190 89 1971

Hellstrom, G The activity of glutamic-oxalacetic and glutamicpyruvic transaminase (GOT and GPT), ornithine-carbamoyl-transferase (OCT) and alkaline phosphatase (AP) in serum in closed liver injury Acta chir scand. 131 485 1966

Henley K. S., Wiggins H. S., Pollard, M Dullaert, E The transaminase content of parenchymatous liver cells. Gastroenterology 36 1 1959.

Henry P D Bloor C. M., Sobel, B E. Increased serum creatine phosphokinase activity in experimental pulmonary embolism Amer J Cardiol. 26 151 1970

Hess, B Walter S I. Chromatographic dif ferentiation of lactate d hydrogenase of human tissue and serum. Ann. N Y Acad. Sci. 94 890 1961

Hess J W MacDonald, R. P Serum creatine phosphokinase ctivity new diagnostic id

in myocardial and skeletal muscle disease. J Mich. med. Soc. 62 1095, 1963.

Hess, J W MacDonald, R. P Frederick, R. J Jones, R. N Neely J Gross, D Serum creatine phosphokinase (CPK) activity in disorders of heart and skeletal muscle. Ann. intern. Med. 61 1015 1964.

Hess, J W Murdock, K. J Natho G J W Creatine phosphokinase. A spectrophotometric method with improved sensitivity Amer J clin. Path. 50 89 1968.

Hill, B. R.. Further studies of the fractionation of lactic dehydrogenase of blood. Ann. N Y Acad. Sci. 75 304, 1958.

Hosty T A., Noto, T A. A clinicopatholog evaluation of serum lactic dehydrogenase (LDH) isoenzymes. Amer J clin. Path. 50 606 1968.

Hughes, B P.. A method for the estimation of serum creatine kinase and its use in comparing creatine kinase and aldolase ctivity in normal and pathological sera. Clin. chim. Acta 7 597 1962.

Jordan, W C., White, W A standard method for determination of the isoenzymes of lactat dehydrogenase in human serum. Clin. chim. Acta 16 457 1967

Kannel, W B., McNamara, P M., Feinleib, M., Dawber T R.. The unrecognized myocardial infarction. Fourteen-year follow-up experience in the Framingham Study Geriatrics 25 75, 1970.

Kaplan, N O Ciotti, M. M. Evolution and dif ferentiation of dehydrogenases. Ann. N. Y Acad. Sci. 94 701, 1961.

Kar N C Pearson, C. M.. Activation f creatine phosphokinase by sulphydryl compounds in nor mal and muscular dystrophy sera. Proc. Soc. exp. Biol. (N Y.) 118 662, 1965 a.

Kar N. C Pearson, C. M.. Creatine phosphokinase isoenzymes in muscle in human myopathies. Amer J clin. Path. 43 207 1965 b.

Karl, W F Peters, T Thermal stability of lactic dehydrogenase from human tissues. Amer J clin. Path. 47 171, 1967

Karmen, A. F Wroblewski, F LaDue, J S. Transaminase activity in human blood. J clin. Invest. 34 126, 1955

Kerppola, W Nikkilä, E. A., Pitkänen, E. Serum glucose-6-phosphate dehydrogenase in the diag nosis of myocardial infarction. Comparison of ts clinical value with that of glutamic-oxalacetic transaminase. Acta med. scand. 166 17 1960

Kibe, O., Nilsson, N. J Observations on the diagnostic and prognostic value of some enzyme tests in myocardial infarction. Acta med. scand. 182 507 1967

Kierkegaard Hansen, A., Kierkegaard-Hansen, G., Creatine phosphokinase determination in myocardial infarction. Dan. med. Bull. 16 53, 1969.

Kirby B. J McNicol, M. W Acid-base status in acute myocardial infarction. Lancet 2 1054, 1966.

Knights, E. M., Whitehouse, J L., Hue, A. C., Santos, C. L. Serum guanase determination A liver function test. J Lab. clin. Med. 65 355, 1965.

Konttinen, A. Alpha-hydroxybutyric dehydrogenase in the detection of myocardial infarction. Lancet 2 556, 1961.

Konttinen, A., Halonen, P I Serum alphahydroxybutyric dehydrogenase (HBD) in myocardial infarction. Comparison with glutami oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH) Amer J Cardiol. 10 525, 1962.

Konttinen, A Halonen, P L Serum creatine phosphokinase and alpha-hydroxybutyric dehydrogenase activities compared with GOT and LDH in myocardial infarction. Cardiologia (Basel 42 86, 1963.

Konttinen, A Rajasalmi, M Paloheimo, J Serum enzyme activities in endotoxin shock. Amer J Physiol. 207 385 1964.

Konttinen, A Lindy S. Denaturation of lactic dehydrogenase isoenzymes and its clinical pplication. N ture 208 782, 1965.

Konttinen, A A further simplified method of ornithin carbamoyltransferase measurement. Clin. chim. Acta 21 29 1968.

Konttinen, A Hupli, V Louhija, A., Härtel, G Origin of elevated serum enzyme activities after direct-current countershock. New Engl. J Med. 281 231, 1969

Konttinen, A Härtel, G Louhija, A. Multiple serum enzyme analyses in chronic alcoholics. Acta med. scand. 188 257 1970.

Konttinen, A., Hupli, V Salmenkivi, K. The diagnosis of hepatobiliary diseases by serum enzyme analyses. Acta med scand. 189 529 1971.

Konttinen, A., Somer H. Determination of serum creatine kinase isoenzymes in myocardial infarction. Amer J Cardiol. 1972 in press.

Kraus, A. P Neely C. L. J Human erythrocyte lactate dehydrogenase Four genetically deter mined variants. Science 145 595 1964.

LaDue, J S., Wroblewski, F Karmen, A.. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science 120 497 1954.

LaDue, J S., Burckhardt, D Nydick, I. Enzymatic assessment of myocardial damage. Geriatrics 22 184 1967

Latner A. L., Skillen, A. W The heat stability index of lactate dehydrogenase in cardiac infarction. Proc. Ass. clin. Biochem. 2 100, 1963

Latner A. L., Turner D M. Clinical application of the effect of acetone on serum lactate dehydrogenase. Lancet 1 1293, 1963

Latner A. L., Turner D M. Quantitative assay of lactate dehydrogenase isoenzymes by reflectance densitometry Clin. chim. Acta 15 97 1967

Lauryssens, M. G Lauryssens, M. J Zondag, H. A. Electrophoretic distribution pattern of lactate dehydrogenase in mouse and human muscular dystrophy Clin. chim. Acta 9 276, 1964.

Lehmann, F G Schneider K. W Menge H. Die Bestimmung von organspezifischen Enzymen. Kreatinphosphokinase und Myokinase. Enzym. biol. clin. 6 36, 1966

Lehmann, F G Schneider K. W Die enzymatische Diagnostik des Herzinfarktes. IV Mitteilung Serumenzymmuster bei Herzinfarkt. Enzym. biol. clin. 6 66, 1966.

Leluan, G Determination de l'activite ornithine carbamyl-transferasique dans le serum. Path. et Biol. 3 567 1965

Levine, M., Israel, H. L., Fisher G R. LDH and SGOT levels in pulmonary embolism. *In* Biochemical Clinics. No. 4. The Lung. ed. L N Kugelmass. New York, R. H. Donnelly Corp 1964.

Lindberg, H. A., Berkson, D M., Stamler J Poindexter A. Totally asymptomatic myocardial infarction An estimate of its incidence in the living population. Arch. intern. Med. 106 628, 1960

Linde, S A comparison between the enzyme patterns (GO-T GP T LD) in serum and tissue extracts in cardiac and hepatic diseases. Scand J clin. Lab Invest. 10 303 1958

Lindy S Konttinen, A Reduced nicotinamide-adenine dinucleotide and pyruvate in urea denaturation of lactic dehydrogenase isoenzymes. Nature 209 79 1966

Lindy S., Konttinen, A The effect of pyruvate on urea-induced inhibition of lactic dehydrogenase isoenzymes Clin chim Acta 14 615 1966 b

Lindy S., Konttinen, A Clinical pplicability of urea LDH test in various pyruvate concentrations. Clin. chim. Acta 17 223, 1967 a.

Lindy S Konttinen, A. Urea-stabl lactate dehydrogenase *as an index of cardiac isoenzymes* Amer J Cardiol. 19 563, 1967 b

Lipman, B S., Massie, E. Clinical Scalar Electrocardiography Ed. 5 Year Book Med. Publ. Chicago 1965

Ljungstrom, B Johansson, B. W Sievers, J Arterial pO_2, pCO_2, pH and standard bicarbonate *in patients with an acute myocardial infarction.* Cardiologia (Basel) 51 138 1967

Logue, R. B Rogers, J V Jr Gay B B. Jr Subtle roentgenographic signs of left heart failure Amer Heart J 65 464, 1963.

Logue, R. B Hurst, J W Clinical recognition of coronary atherosclerosis and its complications. *In* The Heart. *J W Hurst and R. B.* Logue (ed). McGraw Hill, New York 1966.

Lorentz, K., Adlung, J Ritter U Untersuchungen zur Ornithin-Carbamyl-Transferase-Aktivitat im Serum nach Herzinfarkt. Arch. klin. Med. 214 45 1967

Lubran, M., Jensen, W E. Determination of LDH isoenzymes in serum a urea inhibition method compared with an electrophoretic method. Clin. chim. Acta 22 125, 1968

Madritsch, K. Die Myokinase in der Diagnostik des Herzinfarktes. Schweiz. med. Wschr 98 646 1968.

Mahowald, T A., Noltmann, E. A., Kuby S. A. *Studies on adenosinetriphosphate* transphosphorylases III. Inhibition reactions. J biol. Chem. 237 1535, 1962.

Markert, C. L., Møller F Multiple forms of enzymes Tissue, ontogenetic and species specific patterns. Proc. nat. Acad. Sci. (Wash.) 45 753, 1959

Markert, C. L. Lactate dehydrogenase isoenzymes Dissociation and recombination of subunits. Science 140 1329 1963

Meister A. Reduction of alpha gamma-diketo *and alpha beta acids catalyzed by muscle* preparations and by crystalline lactic dehydrogenase. J biol. Chem. 184 117 1950

Menache, R., Rubinstein, I Gaist, L., Marziuk, I. Creatine kinase isoenzymes in normal and pathological sera. Clin. chim. Acta 19 23 1968.

Møller C E., Raabo, E. Diagnostic use of fractionated *lactic dehydrogenase activity (LDH)* in myocardial infarction. Acta med. scand. 175 31, 1964.

Moretti, G Ballan, P Demange G *Staeffen, J.* Un nouveau test de cytolyse hepatique le dosage de l activite ornithine-carbamyltransferasique du serum. Presse méd. 67 2353, 1959.

Muggli, A. LDH Isoenzyme in der Diagnose des Herzinfarktes. Vergleichende Untersuchungen mit Cellogel Elektrophorese, DEAE-Sephadex und HBDH Bestimmung. *Enzym* biol. clin. 9 401 1968

Naeverson, M. A. Metabolic acidosis in acute myocardial infarction. Brit. med. J 2 383 1966

Naftalin, L., Child, V J Morley D. A. Observations on the site of origin of serum gamma-glutamyl-transpeptidase. Clin chim. Acta 26 297 1969

Nisselbaum, J S Schlamowitz, M., Bodansky O Immunochemical studies of functionally similar enzymes. Ann. N Y Acad. Sci. 94 970, 1961.

Nussen, N L, Ranlov P Weis-Fogh, J., Evaluation of four different serum enzymes in the diagnosis of acute myocardial infarction. Brit. Heart J 27 520, 1965.

Nutter D O Trujillo, N P Evans, J M., The isoenzymes of lactic dehydrogenase. I. Myocardial infarction and coronary insufficiency Amer Heart J 72 318, 1966.

Nydick, L, Ruegsegger P Wroblewski, F LaDue, J S. Variations in serum glutamic oxalacetic transaminase activity in experimental and clinical coronary insufficiency pericarditis and pulmonary infarction. Circulation 15 324, 1957

Nygren, A. Serum creatine phosphokinase activity in chronic alcoholism, in connection with acute alcohol intoxication. Acta med. scand. 179 623, 1966.

Okinaka, S., Sugita, H., Momoi, H., Toyokura, Y Watanabe, T Ebashi, F Ebashi, S. Cysteine-stimulated serum creatine kinase in health and disease. J Lab. clin. Med. 64 299 1964.

Oliver I. T A spectrophotometric method for the determination of creatine phosphokinase and myokinase. Biochem. J 61 116 1955

Pagliaro, L., Notarbartolo, A. Alpha-hydroxy butyric dehydrogenase in the diagnosis of myocardial infarction. Lancet 1 1043, 1962.

Pain, M. C. F Stannard, M., Sloman, G Disturbances of pulmonary function after acute myocardial infarction. Brit. med. J 2 591 1967

Paloheimo, J A., Ikkala, E. Serum lactic dehydrogenase activity and isoenzyme patterns in some haematological diseases. Acta med. scand. 177 115 1965.

Paloheimo, J A., Pitkänen, E Elevated lactic dehydrogenase (LDH) activity and the lactic dehydrogenase isoenzyme pattern of serum. Ann. Med intern. Fenn 54 129 1965.

Papadopoulos, N M Kintzios, J A Quantitative electrophoretic determination of lactate dehydrogenase isoenzymes Amer J clin. Path. 47 96 1967

Pathy M S Clinical presentation of myocardial infarction in the elderly Brit. Heart J 29 190 1967

Pearse, A G E Histochemistry Theoretical and Applied. J and A. Churchill, London. Ed. 2, 1960.

Pearson, C. M., Chowdury S. R., Fowler W H. Biochemical detection and histological study of muscular dystrophy in the preclinic state. J clin. Invest. 40 1070, 1961

Perkoff, G T.. Demonstration of creatine phosphokinase in human lung tissue. Arch. intern. Med. 122 326, 1968.

Perloff, J K. The recognition of strictly posterior myocardial infarction by conventional scalar electrocardiography Circulation 30 706, 1964.

Peters, T Davis, J S. Serum heat-stable lactate dehydrogenase in the diagnosis of myocardial infarction. J Amer med. Ass. 209 1166 1969

Pfleiderer G Wachsmuth, E. D.. Alters- und funktionsabhängige Differenzierung der Lactat dehydrogenase menschlicher Organe. Biochem. Z. 334 185 1961

Plagemann, P G W Gregory K. F Wroblewski, F The electrophoretically distinct forms of mammalian lactic dehydrogenase. II. Properties and interrelationships of rabbit and human lactic dehydrogenase isoenzymes. J biol. Chem. 235 2288, 1960.

Plagemann, P G W Gregory K. F Wroblewski, F Die elektrophoretisch trennbaren Lactat-dehydrogenasen des Säugetieres. III. Einfluss der Temperatur auf die Lactat-dehydrogenasen des Kaninchens. Biochem. Z. 334 37 1961.

Plummer D. T Elliott, B. A., Cooke, K. B., Wilkinson, J H. Organ specificity and lactate-dehydrogenase activity 1 The relative activities with pyruvate and 2-oxobutyrate of electrophoretically separated fractions. Biochem. J 87 416, 1963 a.

Plummer D. T Wilkinson, J H. Organ specificity and lactate-dehydrogenase activity 2. Some properties of human heart and liver preparations. Biochem. J 87 423 1963.

Plummer D. T Wilkinson, J H Withycombe, W A. The effect of urea on the activities of lactate dehydrogenase preparations. Biochem. J 89 48P 1963 b

Pojer, J Ninger E., Tovarek, J Changes in serum isocitrate dehydrogenase in myocardial infarction. Enzym. biol. clin. 3 184, 1963.

Polachek, A. A., Zoneraich, S., Zoneraich, O Sass, M. Pulmonary infarction and serum lactic dehydrogenase. J Amer med. Ass. 204 811 1968.

Preston, J A., Batsakis, J G Briere, R. O Serum alpha-hydroxybutyrat dehydrogenase. A clinical and laboratory evaluation in patients with myocardial infarct. Amer J clin. Path. 41 237 1964.

Preston, J A., Briere, R. O Batsakis, J G Rapid electrophoretic separation of lactate de-

hydrogenase isoenzymes on cellulose acetate. Amer J clin. Path. 41 256 1963 a.

Preston, J A., Batsakis, J G Briere, R. O Taylor R. V Serum creatine phosphokinase. A clinical and laboratory evaluation. Amer J clin. Path. 44 71, 1965 b

Prorer S., Naimi, S. Acute and chronic coronary heart disease. Progr cardiovasc. Dis. 5 1 1963.

Pruitt, R. D Dennis, E. W Kinard, S. A. The difficult electrocardiographic diagnosis of myocardial infarction. Progr cardiovasc. Dis. 6 85, 1963.

Pyörälä, K., Gordin, R., Konttinen, A., Telivuo, L. Serum enzymes after cardiac surgery Acta med. scand. 1 4 361 1963

Ravens, K. G Gudbjarnason, S Cowan, C. M., Bing, R. J Gamma-glutamyltranspeptidase in myocardial infarction. Clinical and experimental studies. Circulation 39 693, 1969

Reichard, H. GOT och GPT vid hjärtsjukdom. Opusc. med. (Stockh.) 4 165, 1959

Reichard, H. Ornithine carbamyl transferase ac tivity in human tissue homogenates. J Lab. clin. Med. 56 18, 1960.

Reichard, H. Studies on ornithine carbamoyl transferase activity in blood Methodologic, experimental and clinical investigation. Acta med. scand. Suppl. 390, 1962.

Resnik, W H. The significance of prolonged anginal pain (preinfarction angina). Amer Heart J 63 290 1962

Reynoso, G Backus, J A., Hosler M A. LDH fraction gives clue to infarction. J Amer med. Ass 209 640 1969

Richman, S M Delman, A. J Grob, D Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes Amer J Med 30 211 1961

Richterich. R Burger A., Weber H Die Inaktivierung der Lactat Dehydrogenase durch Harnstoff I Selektiv Hemmung der elektrophoretisch langsam wandernden Isoenzyme Hel physiol pharmacol Acta 20 C78 1962

Richterich. R., Burger A. Preferential urea in activation of lectrophoretically slow-migrating lactic dehydrogenase isoenzymes H lvet. phy siol. pharmacol Acta 21 59 1963.

Richterich, R., Schafroth, P Aebi, H. A study of lactic dehydrogenase isoenzyme pattern of human tissues by adsorption-el tion on Sephadex DEAE. Clin chim. Acta 8 178 1963

Roberts, W M. Blood phosphatase nd van den Bergh reaction in differentiat on f several types of jaundice Brit med J 1 734 1933

Roman, W Quantitativ estimat on of lactat dehydrogenase isoenzymes in serum I Rev ew of methods and distribution in human tissues Enzymologia 36 189 1969

Roman, W Oon, R. C. S Gan, R. T H., Ruys, J Quantitati e estimation f lactate dehydrogenase isoenzymes in serum. II. A simple routine method for the separation of the isoenzymes by heat stability Enzymologia 36 333, 1969

Romslo I. A simple method of preserving serum OCT-acti ity Clin. chim. Acta 36 264 1972.

Rosalki, S. B., Wilkinson, J H. Reduction of alpha-ketobutyrate by human serum. Nature 188 1110 1960

Rosalki, S. B. Alpha-hydroxybutyrate dehydrogenase activity of human tissue homogenates. Clin. chim. Acta 8 415 1963 a.

Rosalki, S. B Serum alpha-hydroxybutyrate dehydrogenase a new test for myocardial infarc tion. Brit. Heart J 25 795, 1963 b.

Rosalki, S. B Creatine phosphokinase isoenzymes. Nature 207 414 1965

Roseman, M. D Painless myocardial infarction A review of the literature and analysis of 220 cases. Ann. intern. Med. 41 1 1954.

Rossi, G F Ligas, A. Importance of the changes in enzyme activity for early diagnosis of myocardial infarct. Pathologica 56 77 1964

Rutenberg, A. M Goldbarg, J A., Pineda, E. P Serum gamma-glutamyl transpeptidase activity in hepatobiliary pancreatic disease. Gastroenterology 45 43, 1963.

Sasahara, A A., Cannilla, J E., Morse, R. L., Sidd, J J Tremblay G M. Clinical and physiologic studies in pulmonary thromboembolism. Amer J Cardiol. 20 10 1967

Sayre, F W Hill, B R. Fractionation of serum lactic dehydrogenase by salt concentration gradient elution and paper electrophoresis Proc Soc. exp. Biol. (N Y) 96 695 1957

Schneider K. W Heuse E R Die Diagnostische Bedeutung einer erhöhten Kreatin-Phosphokinase-Aktivität im Serum Dtsch. med Wschr 88 520 1963

Schneider K. W Lehmann, F G Das Verhalten von GOT LDH, alpha-HBDH und CPK beim Herzinfarkt. Enzym biol clin 6 .3 1966.

Schneider K. W Lehmann, F G Schering, G Die enzymatische Diagnostik des Herzinfarktes III Mitteilung LDH Isoenzyme beim Herzinfarkt Enzym biol clin 6 5., 1966

Schreiber F K. Myokinasebestimmung in der Diagnostik des Herzinfarkts Klin. Wschr 4. 4 8 1964

Shubin, H Weil, M H Acute elevation of serum transaminase and lactic dehydrogenase during circulatory shock Amer J Cardiol. 11 327 1963

Sigma Tentative Technical Bulletin No. 40-UV Revised February 1967 Published by Sigma Chemical Company St. Louis, USA, 1967

Simonson, E., Tuna, N Okamoto, N Toshima, H. Diagnostic accuracy of the vectorcardiogram and electrocardiogram. A cooperative study Amer J Cardiol. 17 829 1966.

Sjövall, K., Voight, A. Creatine-phosphotransferase isoenzymes. Nature 202 701 1964.

Smith, A. F Serum-enzymes in myocardial infarction. Lancet 2 1143, 1964.

Snow P J D Jones, A. M., Daber K. S. A clinico-pathological study of coronary disease Brit. Heart J 18 435 1956

Sodi Pallares, D Bisteni, A., Medrano, G A Ayola, C. Electrocardiography and vectorcardiography Clinical Cardiopulmonary Physiology New York Grune & Stratton, Inc. 1960.

Sodi Pallares, D Medrano G A., De Micheli, A Testelli, M. R., Bisteni, A. Unipolar QS morphology and Purkinje potential of the free left ventricular wall. The concept of electrical endocardium. Circulation 23 836, 1961.

Somer H., Konttinen, A. A method allowing the quantitation of serum creatine kinase isoenzymes. Clin. chim. Acta 36 531, 1972.

Sorensen, N S., Creatine phosphokinase in the diagnosis of myocardial infarction. Acta med scand. 174 725 1963.

Sterkel, R. L., Spencer J A., Wolfson, S. K. Jr Williams-Ashman, H. G Serum isocitric dehydrogenase activity with particular reference to liver disease. J Lab clin. Med. 52 176, 1958.

Stevens, L. E., Burdette, W J Enzymati levels in pulmonary infarction. Arch. Surg. 88 705 1964.

Strandjord, P E., Thomas, K. E., White, L. P Studies on isocitric and lactic dehydrogenase in experimental myocardial infarction. J clin. Invest. 38 2111, 1959

Strandjord, P E., Clayson, K. J Diagnosis f acute myocardial infarction on basis of heat stable serum lactic dehydrogenase J Lab. clin. Med. 58 962, 1961

Strandjord, P E., Clayson, K. J Freier E. F Heat stable lactate dehydrogenase in the diagnosis of myocardial infarction. J Amer med. Ass. 182 1099 1962.

Strandjord, P E. Serum ornithine carbamoyl transferase activity an automati assay In Technical Manual Workshop on Clinical Enzymology Chicago American Society of Clinical Pathologists, 1964.

Strandjord, P E., Clayson, K. J., An automated method for the determination of total lactate dehydrogenase, heat-stable lactate dehydrogenase isoenzyme-1, and hydroxybutyrate dehydrogenase. J Lab. clin. Med. 67 131, 1966 a.

Strandjord, P E., Clayson, K. J Diagnostic enzymology with particular reference to heart and liver Postgrad. Med. 39 A-60, 1966 b

Stuart, J Crawford, I. C., Forshall, J Owen, J A. Serum hydroxybutyrate dehydrogenase in myocardial infarction. Brit. med. J 1 423, 1965

Swaiman, K. F Awad, E. A. Creatine phosphokinase and other serum enzyme activity after controlled exercise. Neurology (Minneap.) 14 977 1964.

Tanzer M. L Gilvarg, C. Creatine and creatine kinase measurement. J bi l. Chem. 234 3201 1959

Ulrich, J Kamaryt, J Zarvorka, Z. The importance of the evaluation of isoenzymes of lactate dehydrogenase in ischemic diseases of the heart. Cor et vasa (Praha) 7 294, 1965.

Valencia, A., Burgess, J H. Arterial hypoxemia following acute myocardial infarction. Circulation 40 641, 1969

Valentine, P A., Fluck, D C., Mounsey J P D Reid, D., Shillingford, J P Steiner R. E. Blood-gas changes after acute myocardial infarction. Lancet 2 837 1966.

Van der Helm, H. J A simplified method f demonstrating lactic dehydrogenase isoenzymes in serum. Clin. chim. Acta 7 124 1962.

Van der Helm, H. J Zondag, H. A., Hartog, H. A. Ph., van der Kool, M. W Lactic dehydrogenase isoenzymes in myocardial infarction. Clin. chim. Acta 7 540 1962.

Van der Helm, H. J Zondag, H. A., Klein, F On the source of lactic dehydrogenase in cerebrospinal fluid. Clin. chim. Acta 8 193, 1963.

Van der Veen, K. J Willebrands, A. F., Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera. Clin. chim. Acta 13 312, 1966.

Velez-Garcia, E., Hardy P Dioso, M., Perkoff, G T Cysteine-stimulated serum creatine phosphokinase unexpected results. J Lab. clin. Med. 68 636 1966.

Vesell, E S Bearn, A. G Localization of lactic acid dehydrogenase activity in serum fractions. Proc. Soc. exp Biol. (N Y) 94 96, 1957

Vincent, W R., Rapaport, E. Serum creatine phosphokinase in the diagnosis of acute myocardial infarction. Amer J Cardiol. 15 17 1965

Wacker W E. C., Ulmer D D Vallee, B. L. Metalloenzymes and myocardial infarction. II. Malic and lactic dehydrogenase activities and

zinc concentrations in serum. New Engl. J Med. 255 449 1956.

Wacker W E. C., Rosenthal, M., Snodgrass, P J Amador E. A triad for the diagnosis of pulmonary embolism and infarction. J Amer med. Ass. 178 108 1961

Warburton, F G Bernstein, A., Wright, A. C. Serum creatine phosphokinase estimations in myocardial infarction. Brit. Heart J 27 740 1965.

Warburton, F G Allan, E., Laing, G S Wadde car J Increased lactate dehydrogenase 3 in serum after myocardial infarction. Nature 215 287 1967

Welshman, S. G Rixon, E. C. Colorimetric estimation of lactic dehydrogenase isoenzymes by urea inhibition. Clin. chim. Acta 19 121, 1968

West, M., Gelb, D Pilz, C. G Zimmerman, H. J Serum enzymes in disease VII. Significance of abnormal serum enzyme levels in cardiac failure. Amer J med. Sci. 241 350 1961

West, M., Eshchar J Zimmerman, H. J Serum enzymology in the diagnosis of myocardial infarction and related cardiovascular conditions. Med. Clin. N Amer 50 171 1966.

Wexler B. C. Serum CPK activity following isoproterenol-induced myocardial infarction in male and female rats with and without arteriosclerosis Amer Heart J 79 69 1970

White, L. P Serum enzymes. I Serum lactic dehydrogenase in myocardial infarction. New Engl. J Med. 255 984 1956.

Wieland, T Pfleiderer G Nachweis der Heterogenität von Milchsäure-Dehydrogenasen verschiedenen Ursprungs durch Trägerelektrophorese Biochem. Z 329 112, 1957

Wieland, T Pfleiderer G Ortanderl, F Über die Verschiedenheit der Milchsäuredehydrogenasen III *Vergleiche der Milchsäuredehydrogenasen* aus verschiedenen Rattenorganen. Biochem. Z. 331 103 1959

Wieme R. J An improved technique of agar gel electrophoresis on microscope slides Clin chim. Acta 4 317 1959

Wieme R J an Maercke, Y The fifth (electrophoretically slowest) serum lactic dehydrogenase as an index of liver injury Ann N Y Acad. Sci. 94 898 1961

Wieme, R. J Diagnostic aspects of serum LDH isoenzymes Postgrad Med 35 A 38, 1964

Wieme, R. J Agar gel electrophoresis Elsevier Amsterdam, 1965

Wieme, R. J Improved gel support for electrophoresis of LDH isoenzymes Clin chim Acta 13 138 1966

Wilkinson, J H. An introduction to diagnostic enzymology Williams & Wilkins, Baltimore, 1962.

Wilkinson, J H. Isoenzymes. E. & F N Spon Ltd, London, 1965

Wilson, A. C., Cahn, R. D Kaplan, N O Functions of the two forms of lactic dehydrogenase in the breast muscle of birds Nature 197 331 1963.

Withycombe, W A., Plummer D T Wilkinson, J H. Organ specificity and lactate-dehydrogenase activity Biochem. J 94 384, 1965

Wood, P Acut and subacut coronary insufficiency Brit. med. J 1 1779 1961.

Woods, I. D Laurie W Smith, W G The realiability of the electrocardiogram in myocardial infarction. Lancet 2 265, 1963

Wright, E. J Cawley L. P Eberhardt, L. Clinical pplication and interpretation of the serum lactic dehydrogenase zymogram. Amer J clin. Path. 45 737 1966.

Wroblewski, F LaDue, J S Lactic dehydrogenase activity in blood. Proc. Soc. exp. Biol. (N Y) 90 210, 1955

Wroblewski, F LaDue J S. Serum glutamic oxalacetic aminopherase (transaminase) in hepatitis. J Amer med. Ass. 160 1130 1956 a.

Wroblewski, F LaDue, J S. Serum glutamic pyruvic transaminase in cardiac and hepatic disease. Proc. Soc. exp. Biol. (N Y) 91 569 1956 b.

Wroblewski, F The clinical significance of transaminase activities in serum. Amer J Med. 27 911, 1959

Wroblewski, F Ross, C Gregory K. Isoenzymes and myocardial infarction. New Engl. J Med. 263 531 1960

Wroblewski, F Gregory K. F Lactic dehydrogenase isoenzymes and their distribution in normal tissues and plasma and in disease states. Ann. N Y Acad. Sci. 94 912, 1961

Wroblewski, F Serum enzyme and isoenzyme alterations in myocardial infarction. Progr car diovasc Dis 6 63, 1963.

Wust, H Schön, H Berg, G Isoenzyme der Lactatdehydrogenase (LDH) und ihre thermische Inaktivierung in der Diagnose innerer Krankheiten. Klin. Wschr 40 1163 1962

Zimmerman, H J Weinstein, H. G Lactic dehydrogenase activity in human serum J Lab. clin Med 48 607 1956

Zimmerman, H J West, M. Serum enzyme levels in the diagnosis of hepatic disease. Amer J Gastroent. 40 387 1963.

Zundel, W S Tyler F H. The muscular dystrophies New Engl. J Med. 273 537 1965

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A clinical electromyographic and biopsy study

Anni Vilppula

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MUSCULAR DISORDERS IN SOME COLLAGEN DISEASES

A CLINICAL, ELECTROMYOGRAPHIC AND BIOPSY STUDY

BY

ANNI VILPPULA

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Helsinki, March 1972

Antti Vilppula

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MUSCULAR DISORDERS IN SOME COLLAGEN DISEASES

INTRODUCTION

The study presented in this report concerns involvement of skeletal muscle in patients with different types of collagen diseases. Only few quantitative data are available of electrophysiological and histopathological findings and few attempts have been made to correlate these with clinical findings. The most common collagen disease, rheumatoid arthritis, is not included in this study because quantitative electrophysiological (Graudal and Hvid 1959 Moritz 1963) and qualitative histopathological findings in large series of patients have been reported (Sokoloff et al. 1950 Cruickshank 1952). The purpose of this study was, then, to obtain quantitative electrophysiological and histopathological data and to relate them to clinical and laboratory findings in patients with collagen diseases.

SELECTION OF THE PATIENTS

110 patients with different collagen diseases, investigated in the years 1953–1971 in the Laboratory of Clinical Neurophysiology of the University Hospital, Copenhagen, were selected for the present study. Patients who had other concurrent diseases which may cause neuromuscular signs and symptoms such as diabetes, thyrotoxicosis, alcoholism, were not included. Most patients were referred on the suspicion of or for confirmation of muscular involvement. The patients with systemic lupus erythematosus were referred consecutively for the electromyographic study regardless of clinical signs and symptoms of muscular involvement.

AGE, SEX AND DURATION OF THE DISEASE

The material comprises 75 females and 35 males. The age, sex and the duration of the disease are given in Tables 1 and 2.

Table 1. Age and sex of patients with collagen disease.

Disease	Total no of pts.	Females No of pts. total	Females <40 years	Females age at onset years	Males No of pts. total	Males <40 years	Males age at onset years
Polymyositis	21	9	1	22—76	12	3	35—69
Dermatomyositis	15	11	0	42—68	4	1	26—68
Juven.poly-dermat.	7	5	5	2—14	2	2	7—12
Syst.lupus eryth.	28	26	17	12—66	2	0	56—63
Syst.lupus eryth. (?)	7	6	4	16—59	1	1	38
Periarteritis nod. (?)	10	3	1	37—58	7	1	30—63
Syst.scleroderma	11	6	3	5—73	5	4	4—44
Local.scleroderma	3	2	2	7—11	1	1	31
Polymyalgia rheum.	8	7	0	53—73	1	0	65

(?) suggestive but not diagnostic

Table 2. Duration of the disease
(The figures denote the number of patients)

Disease	<3 mo	3 mo — 1 yr	1—5 yrs	>5 yrs
Polymyositis	2	12	5	2
Dermatomyositis	0	7	6	2
Juven poly-dermat.	3	2	1	1
Syst lupus eryth.	0	6	10	12
Syst lupus eryth (?)	0	0		5
Periarteritis nod (?)	1	4	2	3
Syst. scleroderma	2	0	4	5
Localized scleroderma			2	1
Polymyalgia rheum	2	4		

(?) suggestive but not diagnostic

CLASSIFICATION

The original concept of collagen diseases assumed pathology of connective tissue, characterized anatomically by mucoid and fibrinoid changes and pathogenetically by hypersensitivity (Klemperer 1950). Systemic lupus erythematosus, systemic scleroderma and periarteritis nodosa were segregated because the primary pathologic alteration seemed to be fibrinoid changes in collagen fibres. Dermatomyositis was included because of its frequent association with systemic lupus erythematosus and scleroderma. These 4 diseases as well as polymyositis are now generally accepted as »collagen diseases» (Amer rheum. ass., Copeman 1969). There is disagreement as to whether the other rheumatic diseases should be included (Sokoloff 1963).

Based on findings of autoimmune abnormalities Bäumer (1968) suggested that Sjögren's (1933 1951) syndrome and autoimmune thyroiditis could be

classified in the group of collagen diseases. Polymyalgia rheumatica is not included although there are some overlapping features with respect to clinical findings and vascular histopathology Early in this century it was realized that there are cases of collagen diseases which did not fit into a given classification (Steiner 1901—1905) This still applies to a number of patients, e.g. 79 of the 727 patients reported by Tuffanelli and Winkelmann (1961) (see also Pagel and Treip 1955 Gardner 1965 and Hart 1969).

Finally it contributes to the complexity that certain types of collagen diseases have been classified according to the major clinical manifestations. Systemic lupus erythematosus may be classified by haematologists with the group of immunohemolytic anaemias and by neurologists as belonging to polymyositis.

In this study only the classification of polymyositis differs slightly from that generally accepted. Barvik and Walton (1963) included dermatomyositis and other collagen diseases in their group III of polymyositis. I have included only patients of their group I and II and those patients of group IV who did not have florid skin lesions. The patients classified as polymyositis in this study had symmetrical weakness in proximal muscles of the extremities, no or only minor cutaneous involvement, normal or near-normal tendon jerks and no clinical or electrophysiological evidence of neuropathy The patients with severe cutaneous involvement and with weakness, wasting, pain or tenderness in proximal muscles of the limbs, with or without malignity were classified as dermatomyositis. Systemic lupus erythematosus (Dubois 1966, Miescher and Paronetto 1969), scleroderma (Sackner 1966 Korting and Holzman 1967 Shulman 1969) and polymyalgia rheumatica (Vischer et al. 1969 Hunder et al. 1969) were classified conventionally In patients called suggestive of periarteritis nodosa the diagnosis was based on signs and symptoms, laboratory findings, the course of the disease and on the exclusion of other systemic diseases although necrotizing angiitis was not demonstrated by biopsy or autopsy No attempts were made to differentiate classical periarteritis nodosa from hypersensitivity angiitis (Alarcón-Segovia and Brown 1964 O'Duffy et al. 1965 Frohnert and Sheps 1967 Paronetto 1969) The most important clinical findings are summarized in the results at the beginning of each section (pages 12—17).

A short historical review of each of the collagen diseases covered in this study is given in the discussion (pages 26—28).

METHODS

A) EVALUATION OF FORCE

The force of the muscle was graded according to the scale suggested by the Medical Research Council (1943).

B) ELECTROMYOGRAPHY

1 Selection of the muscle for study In most patients weakness and wasting were proximal and one of these muscles was examined by electromyography When electromyographic findings seen on the screen of the oscilloscope seemed to be negative, a second proximal muscle was studied either in the lower or the upper extremity In 6 of 11 patients with systemic scleroderma the muscle selected was beneath the most severely affected region of the skin. When there was no clinical evidence of muscle involvement a proximal muscle in the upper or lower extremity or both was examined.

In 91 patients 1 to 3 proximal muscles of the extremities (brachial biceps, deltoid or quadriceps femoris) were examined, in 15 both proximal and distal muscles, and in 4 (3 of them with scleroderma) only distal muscles (anterior tibial, extensor digitorum communis). The intrinsic muscles of the hand and foot were investigated in 8 patients. 18 patients were reinvestigated once or twice.

2. At least 20 different motor unit potentials (average 41) were recorded in each muscle by means of concentric needle electrodes (DISA type 9013K 0032 and 9013K511 with a platinum leading-off area of 0.07 sq mm) and a 3-channel electromyograph (DISA types 13 A 69 and 14 A 30). The extremity was kept at 34—35°C.

3. The following electromyographic criteria were used as evidence of myopathy ($P<0.05$, Buchthal and Rosenfalck 1963). I) A decrease by at least 20% in the average duration of motor unit potentials re-

corded during weak or moderate effort*). ii) An increased incidence of polyphasic potentials by more than 12 / (Caruso and Buchthal 1965). iii) An interference pattern during full effort with an amplitude less than 2 mV in adults and in children over 10 years of age, less than 1 mV in children 5—8 years old, and less than 0.5 mV in children 2—3 years old. iv) A decrease in the average amplitude of motor unit potentials by at least 40 %.

4 The number of sites was determined within a muscle where there was spontaneous activity of short duration (fibrillation potentials and positive sharp waves) and »pseudomyotonic» bursts. More than two sites with fibrillation potentials or positive sharp waves recorded outside the endplate zone were considered abnormal (Buchthal and Rosenfalck 1966).

C) MUSCLE BIOPSY

1 *Muscle examined.* Muscle biopsies were obtained in 102 of 110 patients, a single biopsy in 65 and 2—5 biopsies in 37 patients. In 94 patients at least 1 biopsy was taken from a proximal muscle. In view of reports that electromyography can cause inflammatory or myopathic lesions (Woolf 1962, Engel 1967), in 96 patients at least 1 biopsy was taken from the muscle contralateral to that examined by electromyography (51) or from another proximal muscle (25) or from the same muscle before electromyographic investigation (12). In 8 patients the biopsy was taken from a distal muscle not investigated electromyographically Only in 6 patients was the biopsy from the same muscle 3—14 days after electromyography In 3 of these the histopathological abnormalities were slight, in 3 moderate or severe.

2. *Preparation* The specimens were fixed in 4 % neutral formalin saline, embedded in paraffine, sectioned at 5µm and stained by haematoxylin-eosin and van Gieson s stain.

In 90 patients the biopsy was suitable for *quantitative evaluation* of fibre diameters. The major and minor axes of 100—300 (average 181) fibres were measured on microphotographs of the transverse sections at a total enlargement of 300 times. The histograms of mean diameters were drawn with intervals of 3.3—6.7 µm.

3. *Evaluation of mean fibre diameter and its scatter* The average fibre diameter and its scatter was compared with findings in 31 proximal muscles (Table 3 Fig. 1) obtained early after death from traffic accidents or from patients without weakness or wasting and without other signs and symptoms of neuromuscular involvement The biopsies from these muscles were treated in the same way as those from the patients.

4 *Findings in normal adult muscle* The histogram of diameters was unimodal and the normal mean diameter in females was 45 µm, SD 6 µm and in males 55 µm SD 5 µm. Deviation of more than 20 from normal was considered pathological. There was no systematic variation with age (16—79 years) or in the different muscles examined. In the individual muscle the standard deviation in µm is a gauge of the variation in diameters. The standard

Table 3. Fibre diameter of skeletal muscles in normal adults[1])

	Females	Males
Number of subjects	7	7
mean ge in years	58 (27—74)	44 (16—79)
number of muscles	14	17
mean diameter	45 µm	55 µm
aratio from muscle t m scle	6 µm, 13 % ± 2.5 %	5 µm, 9 ± 1.6
ange f average in different muscles	33—53 µm	48—65 µm
mean standard deviation	8.5 ± 0.6 µm 19 ± 1 1 %	10 ± 0 6 µm 18 ± 1.3 %
ange f tandard deviation	6.5—14 µm, 13—29 %	6.5—16 µm, 10—30 %

) based on data collected by O Thage from 26 muscles of 9 subjects (vastus medialis, vastus lateralis and rectus femoris) and by F Buchthal nd P Rosenfalck from 5 muscles of 5 subjects (biceps brachii nd pectoralis) 5 biopsies th evidenc f slight hrink ge (4) d with a bimodal distribution (1) not included in the calculation of the erage I every muscle biopsy the mean diameter f 100—200 fibres (mean 180) was measured.

) The normal values of m dur tion nd mpl tude of motor unit potential m scles f om bject f different ge were those btained the Laboratory of Clinical Neurophysiol gy of the Uni ers ty Hospital Copenhagen They were originally published 1957 nd 1962 (Buchthal 1957 Sacco et al 196) The stud es have since been extended and the res lt were kindly made avail bl to me.

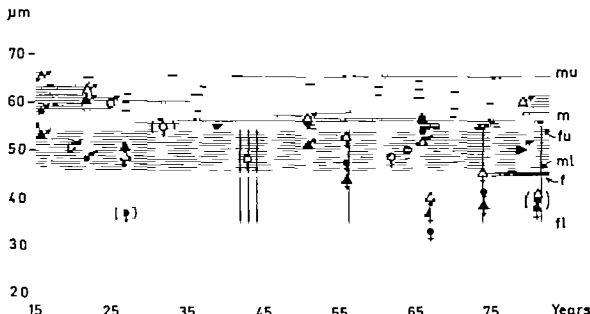


Fig. 1. Mean diameter of muscle fibres in 36 muscles f 16 subjects with ut signs nd symptoms of neuromuscular disease as functio f age. The horizontal lines indicate the ra ge f normal (2 times SD) in males and the vertical lines the range f normal in females.

Biopsies with more tha normal shrinkage (30 %) re given i brackets and were not included in the calculatio *f the mean values nd the standard devi tions.* Data collected by D O Thage from 30 muscles of 10 subjects (△ male, ♁ female, vastus medialis, ♂ male, ♀ female, vastus lateralis ▲ male, ♦ female, rectus femoris) and by Dr F Buchthal and P Rosenfalck from 6 muscles of 6 subjects (♂ male, ♀ female, brachial biceps nd ♂ male, pectoralis) *m, mean value for* muscles f males (mu, upper limit f normal ml, lower l mit of normal). f mean value f muscles f females (*fu, upper limit f normal fl lower limit f normal*).

deviation in per cent of the average diameter indicates whether an increase or decrease in diameters is generalized or concerns some fibres more than others. The standard deviation within a muscle averaged 8.5 µm in females and 10 µm in males. A standard deviation of more than 14 µm in females or 16 µm in males, i.e. more than 30 ‰, was considered abnormal (Fig. 1 Table 3).

5 *Findings in normal infants and children.* The normal mean diameter and its scatter as a function of age was taken from Fig. 4 of Buchthal and Zander Olsen (1970).

6. *Definition of atrophic and hypertrophic fibres* Atrophy and hypertrophy of fibres were defined according to Buchthal et al. (1971). Atrophic fibres were given as the per cent incidence of fibre diameters smaller than the normal mean minus 2 times the standard deviation (M−2×SD). Thus, fibres less than 28 µm in diameter in females and 35 µm in diameter in males are denoted as atrophic. Hypertrophic fibres were given as the per cent incidence of fibre diameters larger than the normal mean plus 2 times the standard deviation (M+2×SD). Thus, fibres more than 62 µm in diameter in females and 75 µm in diameter in males were denoted as hypertrophic. With these definitions, and in view of the variation from one subject to the next 5−6 µm in mean diameter we conclude that more than 17 % atrophic or hypertrophic fibres is abnormal.

7 The *qualitative evaluation* followed closely the criteria given by Greenfield et al. (1957). These criteria are enumerated in Table 4 All biopsies were examined by at least 2 observers. When there was doubt the opinion of a third pathologist was sought. A biopsy was classified as moderately or severely abnormal when at least two of the criteria (given in Tables 4 and 6) showed moderate or severe abnormalities.

RESULTS

A) CLINICAL AND LABORATORY FINDINGS

1 Polymyositis in adults

There were 21 patients with subacute or chronic polymyositis (case report 1 p. 33). All patients had weakness in and nearly all had wasting of proximal muscles of the extremities (Tables 7 8). 12 complained of pain in the same muscles. Flexion of the neck was weak in 12, and 8 of these had normal force of extension of the neck. 9 complained of difficulty in swallowing, 2 in speaking and 1 in chewing. Tendon jerks were normal in 12, increased in 5 and weak in 4. 16 had signs and symptoms from 1 or 2 other organ systems than muscle, most commonly the skin, the joints or the respiratory tract, the remaining 5 had only muscular involvement. 16 patients had elevated sedimentation rates and 15 of these had increased globulin in the electrophoresis of the serum. Serum creatine phosphokinase, lactate dehydrogenase or both were determined in 12 patients and were slightly increased (2 times normal) in 7 markedly increased (20 times normal) in 1. A benign thymoma without clinical or electromyographical evidence of myasthenia was found in one 57-year-old man, and malignant tumours in 2 (a 57-year-old man with a hypernephroma and a 45-year-old woman with a rectal carcinoma).

Electromyography (Table 5). All patients had decreased mean duration of the motor unit potentials and all but 1 had at least one other criterion of myopathy. The one exception, the patient with hypernephroma had as the only finding a markedly decreased mean duration of motor unit potentials in the brachial biceps and femoral rectus muscles. Spontaneous activity was found in 11 of 21 patients.

Muscle histopathology (Tables 4 6). Biopsies were obtained in 21 patients, 14 had moderate to severe and 7 slight abnormalities. Biopsies suitable for quantitative evaluation (19 patients) showed abnormalities in 14 patients. They had either increased (6) or decreased (4) diameter increase in hypertrophic (9) or in atrophic (8) fibres, in scatter of diameter expressed as μm (9) or as per cent (9).

16 of 21 patients had moderate to severe inflammatory usually perivascular changes. The atrophic and hypertrophic fibres were randomly distributed except in 5 patients in whom the atrophy was »patchy». Three quarters had structural changes in the muscle fibres, in one quarter in large areas. Internal nuclei and proliferation of connective tissue occurred in half of the patients.

2. Dermatomyositis in adults

All 15 patients had typical cutaneous involvement, all but 2 had either weakness or wasting or both (Tables 7 8 case report 2, p. 33) and 10 including the 2 without weakness and wasting complained of muscle tenderness. Flexion of the neck was weak in 5 and extension as well in 2. 5 complained of difficulties in swallowing and 1 in chewing. Tendon jerks were normal in 11 increased in 1 and weak or absent in 3. 8 had evidence of arthritis, 4 of respiratory tract and 2 of urinary tract involvement. The sedimentation rate was elevated in all but 1 and serum electrophoresis showed increased globulin in 11. Serum creatine phosphokinase, lactate dehydrogenase or both were taken in 9 patients and were increased in 7. A malignant tumour was found in 3 (a 68-year-old man with gastric carcinoma, a 50-year-old woman with cancer of the breast and a 55-year-old woman with cancer of the ovary).

Electromyography (Table 5). All but 1 patient had a decreased mean duration of motor unit potentials in the first examination and that 1 revealed it in a second examination [illegible] months later. All but 1 had in addition at least one other criterion of myopathy. Spontaneous activity occurred in 5 patients.

Table 4. Findings in the muscle biopsy of 100 patients with collagen disease.
(The figures denot the mber of patients)

	PM			DM			Juven. PM+DM			SLE			PN(?)			SC*			PM RH		
	21 pts.			15 pts.			5 pts.			31 pts.			10 pts.			10 pts.			8 pts.		
	0	(+)	+	0	(+)	+	0	(+)	+	0	(+)	+	0	(+)	+	0	(+)	+	0	(+)	+
Patchy a trophy			5												3			1			
Smallest fibres t the periphery f th fascicell					6				2		1						1				
Increas. No of nuclei	15	3	3	11	3	1	2	1	2	23	5	3	6	3	1	8	1	1	8		
Internal nuclei	3	6	12	7	2	6	2	1	2	21	6	4	6	1	3	7	2	1	6	2	
Cross-striations: normal	5			10			3			22			6			7			8		
Cross-striations: cloudy		3									3						1				
Cross-striations: lost		9	4		4	1		2			6			4			2				
Prol f of connect. tissue	7	5	9	8	4	3	2	2	1	19	4	8	5	3	2	5	1	4	8		
Prolif of fat	16	4	1	10	3	2	3	2		17	8	6	9		1	8	1	1	5	3	
Inflammatory cells: focal	9	5	7	5	2	8	2	1	2	10	12	9	5	2	3	4	2	4	4	4	
Inflammatory cells: diffuse	8	5	8	8	4	3	2	1	2	22	3	6	4	2	4	5	3	2	6	1	1
Inflammatory cells: perivascular	3	7	11	3	1	11		2	3	9	8	14	3		7	1	4	5	2	6	
Vacuoles	17		4	13	1	1	2		3	30		1	9		1	10			8		
Impression of abnormality	0	7	14	1	8	6	0	3	2	2	18	11	2	4	4	1	5	4	3	5	0

Abbreviations PM Polymyositis, DM: Dermatomyositis Juven.PM+DM Juvenile poly- and dermatomyositis, SLE. Systemic lupus erythematosus. PN(?): S ggestive of periarteritis nodosa, SC. Systemic scleroderm PM RH Polymyalgia rheumatica.

0: Normal

(+): Slightly bnormal

+: Moderately or severely abnormal

7 f these without repeated LE-cells but otherwise suggestive of the disease.

*: Patients ith local scleroderma not included.

*: Confined to small areas (+) co fined to large area +

*: Based on qua titative and qualitative findings.

Table 5. Electromyographic findings in 110 patients with collagen disease
(The figures denote the number of patients)

Disease	Total	Motor unit potentials: Duration dimin. ≥20 %	norm.	Amplitude dimin. ≥40 %	norm.	Polyph. >12 %	Spontaneous ct.: di-phas.	pos. sharp	pseudo-myot.» bursts	EMG norm
Polymyositis	21	21	0	15	6	13	11	7	3	0
Dermatomyositis	15	14	1	8	7	9	5	3	3	0
Juven poly-dermat.	7	7	0	1	6	6	3	1	0	0
Syst.lupus eryth.	28	22	5	9	19	11	5	2	2	3
Syst.lupus eryth (?)	7	6	1	3	4	4	0	0	0	0
Periarteritis nod.(?)	10	7	3	4	6	7	2	1	0	2
Syst.scleroderma	11	6	5	3	6	6	2	2	1	1
Local.scleroderma	3	1	2	1	2	1	0	0	0	1
Polymyalgia rheum.	8	6	2	5	3	3	0	0	0	0

(?) suggestive but not diagnostic.
*) 1 patient had increased duration of motor unit potentials.
*) 2 patients had increased amplitude of motor unit potentials.

Table 6. Muscle fibre diameters in 90 patients with collagen disease.

Disease	No. of pts.	N of biopsies	No. of biopsies mean diameter increas.	decreas.	S.D I μm	increased in %
Polymyositis	19	28	10	5	15	13
Dermatomyositis	14	22	7	2	12	5
Juven.poly-dermat.	5	8	1	1	3	4
Syst.lupus eryth.	21	26	11	1	8	5
Syst.lupus eryth.(?)	7	9	3	0	3	3
Periarteritis nod.(?)	9	15	4	2	5	7
Syst. & loc.scleroderma	9	13	3	3	5	4
Polymyalgia rheum.	6	8	2	1	2	1

) A change in mean diameter exceeding 12 μm in females and 10 μm in males.
) Upper limit of normal standard deviation (SD) in adult females 14 μm (29 %) in adult males 16 μm (30 %).
(?) Suggestiv but not diagnostic.

Muscle histopathology (Tables 4 6). Biopsies were obtained in 15 patients 1 had no abnormality 6 had moderate to severe and 8 had slight abnormalities. Biopsies suitable for quantitative evaluation (14 patients) showed abnormalities in 11 patients. They had either increased (3) or decreased (2) diameter increase in hypertrophic (6) or in atrophic (4) fibres, or increased scatter of diameters in μm (7) or in per cent (5).

Moderate to severe inflammatory changes were seen in 13 of 15 patients, mostly localized perivascularly In most patients the trophic and hypertrophic fibres were randomly distributed, in 6 however the smallest fibres were in the periphery of the fasciculi. Cross-striation was lost in one third, in large areas in 1 patient. One third had an increased incidence of internal nuclei.

3 Juvenile dermatomyositis and polymyositis

All 7 patients (4 with dermatomyositis and 3 with polymyositis, case report 3 p. 38) had weakness and 5 had wasting of proximal muscles (Tables 7 8). 3 complained of tenderness and pain in the same muscles. Flexion of the neck was weak in 5 and extension was also weak in 4 2 patients complained of difficulties in swallowing Tendon jerks were normal in 5 and weak in 2. 4 had pronounced and 1 minor cutaneous involvement. 3 patients showed evidence of arthritis and 2 of respiratory tract involvement. All 7 had an elevated sedimentation rate and 4 an increased globulin on serum electrophoresis.

Electromyography (Table 5) All had decreased mean duration of motor unit potentials and at least

Table 7 Number of patients with muscle weakness.

Disease	Average force)	Total	Upper extremities prox.	Upper extremities dist.	Lower extremities prox.	Lower extremities dist.	Both extremities prox.	Both extremities dist.	Norm. force
Polymyositis	3+	21	5	2	3	0	13	1	0
Dermatomyositis	4	15	4		1		7	1	3)
Juven.poly-dermat.	3+	7	1			2	6		0
Syst.lupus eryth. *)	5—	35	4	1	1	1	6	2	24
Periarteritis nod.(?)	3+	10	1				6	3	3
Syst. & loc.scleroderma	4+	14	3	2			1		8
Polymyalgia rheum.	5—	8	2				5		1

) Graded according to the scale of the Medical Research Council 1943

) There was tenderness of the muscles and histopathological and electrophysiological signs of myopathy

) 7 of these without repeated LE-cells, but otherwise suggestive of the disease.

(?) Suggestive but not diagnostic.

Table 8. Number of patients with muscle wasting

Disease	Average wasting prox.	Average wasting dist.	Total	Upper extremities prox.	Upper extremities dist.	Lower extremities prox.	Lower extremities dist.	Both extremities prox.	Both extremities dist.	No wasting
Polymyositis	moder	mild	21	3	4	4	1	13	3	1
Dermatomyositis	moder.	mild	15	4	1			6	1	5
Juven.poly-dermat.	moder	none	7	2				3		1)
Syst.lupus eryth.)	mild	mild	35	3	3	2		8	4	21
Periarteritis nod.(?)	moder	mild	10	1	1	1		6	4	2
Syst. & loc.scleroderma	mild	mild	14		4			5	2	6
Polymyalgia rheum	mild	mild	8	3	1			2		3

*) One not estimated because of oedema.

) 7 of these without repeated LE-cells, but otherwise suggestive of the disease.

(?) Suggestive but not diagnostic.

one other criterion of myopathy. Spontaneous activity occurred in 3 patients.

Muscle histopathology (Tables 4 6). Biopsy was obtained in 5 patients; 2 had moderate to severe and 3 had slight abnormalities. All biopsies were *suitable for quantitation and showed abnormalities* in all but 1. They had either increased (1) or decreased (1) diameter, increase in hypertrophic (1) or in atrophic (1) fibres, in scatter of diameters in μm (1) or in per cent (3).

Moderate to severe inflammatory changes were seen in all patients, mostly localized perivascularly. Only in 2 were there changes in the arterial wall (Banker and Victor 1966). The atrophic fibres were mostly randomly distributed, in 2 however confined to the periphery of the fasciculi (Fig. 11 C). Cross-striation was lost in small areas in 2 and vacuoles occurred in 3 patients. Internal nuclei and an increase in sarcolemmal nuclei were seen in 2 patients.

4. Systemic lupus erythematosus

There were 28 patients with systemic lupus erythematosus and 7 patients suspected of this disease (case report 4, p. 38). About a third of the patients had weakness and wasting in proximal muscles (Tables 7 8), 11 complained of pain and 7 of tenderness in the same muscles. Tendon jerks were normal in 25, *increased in 9 and weak in 1. 28 patients had typical* LE-cells at least twice, elevated sedimentation rate and signs and symptoms referable to 2 or more of the organ systems affected in systemic lupus erythematosus (joints or skin, gastrointestinal, haematological, urogenital, pulmonary, cardiac and nervous system). When the joints were involved rheumaserology (Waaler Rose and latex fixation tests) was negative or there were in addition signs and symptoms from 2 other organ systems. In the 3 patients in whom autopsy was performed, the diagnosis was confirmed.

7 patients with signs and symptoms suggestive of systemic lupus erythematosus showed LE-cells once (3 patients) or not at all (4). Only 1 was treated by steroids before the first examination for LE-cells, 1 had in addition signs and symptoms typical of

Sjögren's syndrome (1933, 1951) (keratoconjunctivitis sicca and xerostomia). All had evidence of involvement of at least 3 organ systems. The other laboratory findings were as in the patients with systemic lupus erythematosus.

Electromyography (Table 5) In 28 of 35 patients the mean duration of motor unit potentials was decreased and 23 had at least one other criterion of myopathy Of the remaining 7 patients 1 had a decreased mean duration of motor unit potentials in a second examination 4 years later 3 had increased incidence of polyphasic potentials, one with slightly increased mean duration of motor unit potentials and 3 had normal electromyographic findings. Spontaneous activity occurred in 5 patients.

Muscle histopathology (Tables 4 6) Biopsies were obtained in 31 patients 11 had moderate to severe and 18 slight abnormalities and 2 had normal findings. Biopsies in 28 patients were suitable for quantitation. Abnormalities were found in 22. They had either increased diameter (14), increase in hypertrophic (16) or in atrophic (4) fibres, in scatter of diameter in μm (9) or in per cent (7).

Moderate or severe inflammatory changes were seen in 18 of 31 patients, mostly localized perivascularly Cross-striation was cloudy or lost in small areas in one third and only 1 patient had vacuoles. Changes in the number and sites of the nuclei occurred in only 10 %. Proliferation of connective tissue was present in a quarter and of fat in 20 of the patients. Of 14 patients without clinical signs of muscle involvement 11 had abnormalities in the muscle biopsy (7 slight, 4 moderate).

5 Periarteritis nodosa (7)

10 patients were classified as suggestive of the disease although neither the biopsy nor autopsy showed necrotizing angiitis (case report 5 p. 38): All had febrile episodes, loss of weight, respiratory tract involvement and signs and symptoms referable to at least 3 other organ systems. More than half the patients had episodes of abdominal pain, involvement of joints, skin, urinary tract and of the peripheral or central nervous system. All had elevated sedimentation rate and an increased globulin in serum electrophoresis 7 had leucocytosis, 5 had anaemia and eosinophilia. Most had weakness and wasting in proximal and distal muscles (Tables 7 8) 6 complained of pain and two of tenderness in these muscles. Tendon jerks were normal in 5 increased in 3 and weak in 2.

Electromyography (Table 5). 7 had decreased mean duration of motor unit potentials and at least one other criterion of myopathy In 1 the only finding was an increased incidence of polyphasic potentials and spontaneous activity and 2 had normal findings.

Muscle histopathology (Tables 4 6). Biopsies were obtained in 10 patients, 4 had moderate to severe and 4 slightly abnormal and 2 had normal findings. Biopsies were suitable for quantitation in 9 patients. 6 showed abnormalities, either increased (2), or decreased (2) diameter increase in hypertrophic (2) or in atrophic (4) fibres, in scatter of diameters, in μm (3) or per cent (4)

Moderate or severe inflammatory changes were seen in 7 of 10 patients, mostly localized perivascularly The arterial walls were intact except in 1 patient (Fig 15). Atrophic fibres were randomly distributed except in 3 patients, in whom the atrophy was »patchy» Cross-striation was lost in small areas in 4 Internal nuclei were seen in 3 and proliferation of connective tissue in 2.

6. Systemic and localized scleroderma

There were 11 patients (9 adults and 3 children with systemic and 3 with localized scleroderma (Illustrative case report 6, p. 39). In 8 patients the diagnosis was confirmed by a skin biopsy Half of the patients had weakness and wasting in proximal and distal muscles (Tables 7 8). Tendon jerks were normal in 12 and increased in 2. 7 with systemic scleroderma had evidence of arthritis and 1 showed signs and symptoms typical of Sjögren's syndrome (see p 16). 1 of the patients with local scleroderma had left hemiatrophy

Electromyography (Table 5). In 6 of the 11 patients with systemic scleroderma the mean duration of motor unit potentials was decreased and all but one had in addition at least one other criterion of myopathy Another patient showed two other criteria of myopathy Of the remaining 4 patients, 2 had an increased incidence of polyphasic potentials, one of these in addition spontaneous activity at 5 sites and increased amplitude of motor unit potentials. One had borderline changes and one normal findings. There was no systematic relation of the abnormalities to the site of the skin lesion.

In the 3 patients with localized scleroderma the muscle examined was subjacent to the skin lesion. 1 had electromyographic evidence compatible with myopathy 1 had an increased incidence of polyphasic potentials as the only finding and in 1 patient electromyography was normal.

Muscle histopathology (Tables 4 6). Biopsies were obtained in 10 patients with systemic scleroderma 4 had moderate to severe and 5 slight abnormalities and 1 had normal findings. Biopsies were suitable for quantitation in 8 patients. They showed either increased (1) or decreased (3) diameter increase in hypertrophic (3) or in atrophic (3) fibres, in scatter of diameters in μm (3) or in per cent (4)

Moderate to severe inflammatory changes were

seen in 7 of 10 patients, mostly localized perivascularly. Structural changes in fibres occurred rarely (3 patients). Proliferation of connective tissue was seen in 4 patients. 3 of the patients with systemic scleroderma did not have clinical evidence of muscular involvement. In 2 of these the biopsy showed slight abnormalities.

Biopsy was taken in 2 of the 3 patients with localized scleroderma and showed only slight abnormalities. One biopsy was suitable for quantitation. The diameter was increased as was the incidence of hypertrophic fibres and the scatter in μm.

7. Polymyalgia rheumatica

All 8 patients had an elevated sedimentation rate (32–113 mm/h, mean 65 mm/h), negative rheumaserology and pain in proximal muscles restricting movement in the shoulder and hip girdle (case report 7, p. 40). Most had mild weakness and wasting of these muscles (Tables 7, 8). Tendon jerks were normal in 3, increased in 4 and weak in 1. Only 1 had signs and symptoms of temporal arteritis. 6 patients responded to steroid treatment, 2 others recovered after 1 and 2 years respectively. 7 patients had febrile episodes and in 7 serum globulin, particularly the alpha-2 fraction, was increased (Björkman 1958, Small and Gavrilescu 1963).

Electromyography (Table 5). 6 patients had a decreased mean duration of motor unit potentials and all but 1 had at least one other criterion of myopathy; in 2 patients changes were borderline.

Muscle histopathology (Tables 4, 6). Biopsies were obtained in 8 patients. Considering both quantitative and qualitative evaluation the biopsy was slightly abnormal in 5 and normal in 3. Abnormalities in the fibre diameter were measured in 4 of the 6 patients in whom the biopsy was suitable for quantitation (increased mean diameter (2), increased incidence of hypertrophic (3) or of atrophic (1) fibres and increased scatter of diameters in μm (2) or in per cent (1)). Inflammatory changes were moderate in one, slight in 5 and absent in 2. Other changes were borderline or absent.

B) SUMMARY OF FINDINGS ON ELECTROMYOGRAPHY

The common electromyographic finding in patients with collagen diseases was suggestive of myopathy (Figs. 2–4). This was most frequently observed in proximal muscles. Upper and lower extremities were equally often affected although weakness was noticed more often in the upper extremities. The mean duration of motor unit potentials was decreased in 92 of 110 patients (84 %), most markedly in adult polymyositis; all 43 patients with poly- and dermatomyositis showed a decreased duration of motor unit potentials. The shortening in mean duration is due both to a decreased incidence of potentials of long duration and to the occurrence of shorter potentials than seen in normal muscle, as illustrated in the histograms from the brachial biceps muscle (Fig. 5). The incidence of polyphasic potentials was increased, most pronouncedly in adult polymyositis.

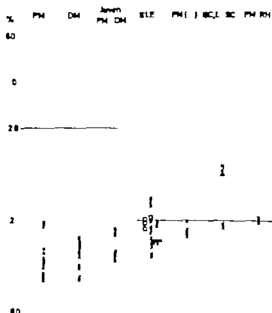


Fig. 2. Mean duration of motor unit potentials (first investigation) in patients with different types of collagen diseases in % of the normal value from subjects of the same age. The horizontal lines represent the lower and the upper limits of normal ($P < 0.05$).
PM. Polymyositis in adults
DM. Dermatomyositis in adults
Juven.PM+DM. Poly- and dermatomyositis in children
SLE. Systemic lupus erythematosus. □ Suggestive, not diagnostic
PN(?): Suggestive of, not diagnostic for Periarteritis nodosa
SC: Systemic scleroderma
L-SC. Localized scleroderma (△)
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Moderate to severe inflammatory changes were

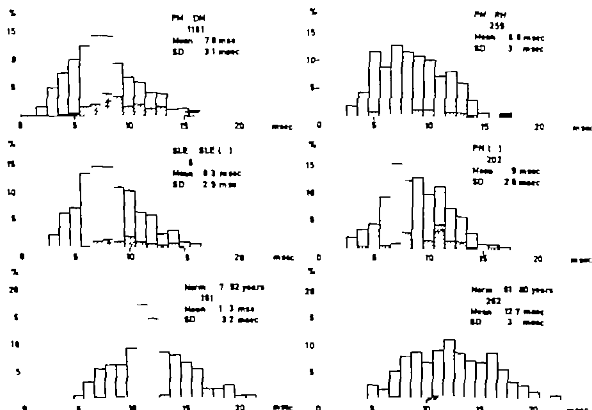


Fig 5 Histograms of the duration f motor unit potentials in the brachial biceps muscle. Left (abov) 25 patients with poly- and dermat myositis (mid) 13 patients with systemic lupus erythematosus, (below) 6 normal subjects f the same age. Right (above) 5 patients with polymyalgia rheumatica (mid) 4 patients with signs and symptoms suggestive f periarteritis nodosa (below) 10 normal subjects of the same ge. The shaded columns denote polyphasic potentials. Only patients were included in whom the mean duration f motor unit potentials was significantly decreased. n. Number of potentials.

other electromyographic criteria suggestive of myopathy

Fibrillation potentials occurred in half positive sharp waves in third of the muscles of patients with adult polymyositis. Fibrillations were seen in one third of muscles in dermatomyositis and were rare in the other groups, as were positive sharp waves.

Pseudomyotonic bursts were recorded in 14 % of patients with polymyositis and in 20 % of patients with dermatomyositis, more rarely in the other groups of collagen diseases.

Electromyographic signs suggestive of myopathy in 6 of the 8 patients with polymyalgia rheumatica deserve special mention because most previous studies did not reveal abnormalities.

In 13 of 18 patients another electromyographic examination several months or years later confirmed findings in the first study In 3 patients with clinical progression (polymyositis, dermatomyositis and systemic lupus erythematosus) abnormalities were more pronounced and in 2 (dermatomyositis), who had improved after steroid treatment, the electromyogram was normal.

C) SUMMARY OF FINDINGS IN THE MUSCLE BIOPSY

1 Quantitated data

i) *The average diameter* (Fig. 6) of the muscle fibres in biopsies from patients with systemic lupus erythematosus was increased, particularly in those patients who had not been treated by steroids (p. 23).

ii) *Hypertrophic and atrophic fibres* (for definition see page 11 Fig 7) In polymyositis, hypertrophic fibres (48 of the patients), occurred as often as

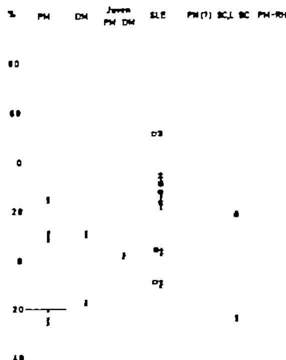


Fig 6 Change in mean diameter of muscle fibres in patients with different types of collagen diseases in % of the normal value from subjects of about the same age and the same sex. The horizontal lines represent the lower and upper limits of normal.
PM. Polymyotitis in adults
DM Dermatomyositis in adults
Juven.PM+DM. Poly- and dermatomyositis in children
SLE. Systemic lupus erythematosus, × treated by steroids, ⊘ not treated by steroid, □ suggestive, not diagnostic
PN(?): Suggestive of not diagnostic for Periarteritis nodosa
SC. Systemic scleroderma
L-SC. Localized scleroderma (△)
PM RH. Polymyalgia rheumatica
Sjögren s syndrome (■)

atrophic fibres (42 % of the patients), and both were increased in only 3 patients. The collagen disease with a consistent change in average diameter (Fig. 6) was systemic lupus erythematosus; the mean diameter was increased due to an excess of hypertrophic fibres particularly in those patients who had not been treated with steroids.

In systemic lupus erythematosus half the patients had an increased incidence of hypertrophic fibres, whereas atrophic fibres were rare (14 % of the patients). In patients with periarteritis nodosa (?)

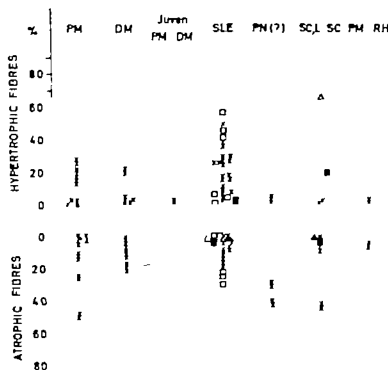


Fig 7 Per cent incidence of hypertrophic and trophic fibres calculated from th histograms of diameters. The dashed lines indicat the limit of the normal range ($p<0.05$).
Hypertrophy Diameters larger tha the normal mean diameter plus 2 times SD
Atrophy Diameters smaller than the normal mean diameter minus 2 times SD
PM. Polymyositis in adults
DM. Dermatomyositis in adults
Juven PM+DM Poly- and dermatomyositis in children
SLE: Systemic lupus erythematosus; □ Suggestive, not diagnostic
PN(?): Suggestive of, not diagnostic for Periarteritis nodosa
SC. Systemic scleroderma
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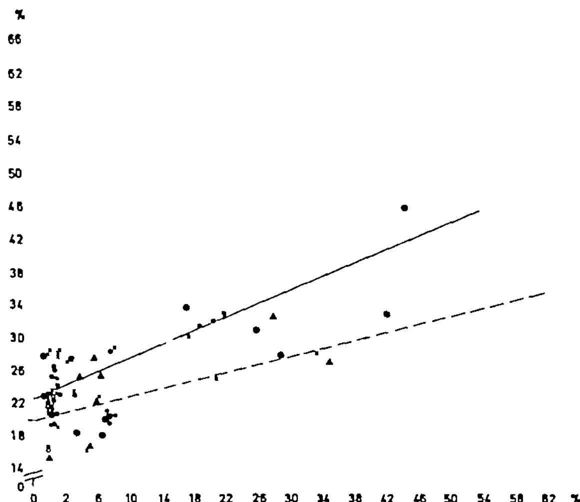


Fig. 8. Scatter f diameter of muscle fibres in per cent (ordinate) as function f the incidence of atrophic fibres (abscissa). (For definition see p. 11. Muscles: Quadriceps fem. 67, brachial biceps 31, deltoid 18, muscles from antebrachium, anterior tibial etc. 13.)

The increase in relative scatter cannot alone be c-counted for by the decrease in average diameter. The full line is the regression line fitting the experimental points. The broken line indicates the increase in relative scatter to be expected in atrophic muscles with normal spread in µm. The dditional increase of the rela ive scatter ctually found reflects an increased scatter in µm in large proportion of the trophic muscles. The difference between the full line and the broken line is significant ($P < 0.001$)

× Poly- and dermatomyositis
○ Systemic lupus erythematosus with 7 cases in whom the diagnosis was uncertain
● Suggestive f periarteritis nodosa
⊗ Scleroderm
▲ Polymyalgia rheumatica
■ Sjögren's syndrome

on the other hand atrophic fibres were frequent (44 of the patients). Except for the 3 patients with polymyositis, none of the biopsies from patients with other collagen diseases showed an increase in the incidence both of hypertrophic and of atrophic fibres.

IIb) *The standard deviation in µm and in per cent* (Table 6): In about a third of the patients (35 of 90) the absolute standard deviation [illegible] the mean diameter was increased indicating that the histogram of diameters included fibres with smaller or larger diameter than normal or with both (Table 6). Provided a symmetrical distribution a muscle with 50 of atrophic fibres would have a mean diameter of 28 µm in a female and 35 µm in a male (p. 11). Assuming a normal standard deviation of 8.5 and 10 µm respectively (p. 11) the relative SD would be 20 %. As to be expected the relative standard devia-

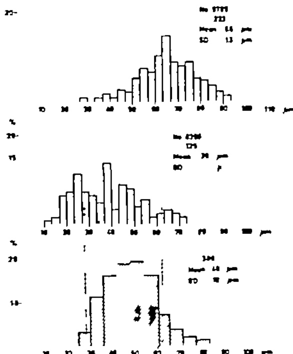


Fig 9 Examples of the distribution of muscle fibre diameters with an increased mean diameter (above) and a decreased mean diameter (middle) as compared to normal (below) (Above): Systemic lupus erythematosus, right rectus femoris muscle (force 5 no wasting, moderat tenderness). Female 35 years of age. (Middle): Symptoms and signs suggestive of periarteritis nodosa, left deltoid muscle (force 1 moderate wasting) Female 64 years of age. (Below): The brachial biceps muscle from three normal females, 43—62 years of age.
The broken lines indicate the average diameter of normal muscle plus and minus 2 times SD
n: Number of muscle fibres.

tion increased with an increasing incidence of atrophic fibres (Fig. 8), but the increase was greater than expected from the decrease in average diameter alone.

iv) *Shape of the distribution curve* In 78 of the 90 patients in whom quantitative data were available, the distribution curve of diameters was unimodal as in normal muscle (Schwalbe and Mayeda 1890 Sissons 1964 Coërs and Hildebrand 1965 and Reske Nielsen et al. 1970) even if displaced toward larger (as in systemic lupus erythematosus) or toward smaller (periarteritis nodosa (?)) diameters (Fig. 9) In the remaining 12 patients the histogram was distributed over an especially large range of diameters, sometimes with a suggestion of two peaks.

2. Qualitative evaluation (Table 4)

i) *Inflammatory reactions* of moderate or severe degree were common except in polymyalgia rheumatica. a) Perivascularly localized inflammatory changes (Fig. 10 A) were most common. b) Inflammatory foci (Fig. 10 B) within or around a single or a small group of muscle fibres occurred frequently in dermatomyositis and scleroderma. c) Diffusely distributed inflammatory reactions (Fig 10 C) were found in half the patients with polymyositis and periarteritis nodosa (?), and in only a fifth of the patients with dermatomyositis and systemic lupus erythematosus.

ii) *Distribution of atrophy* Usually the atrophic fibres were distributed randomly (Fig. 11 A) There were, however exceptions: a) Atrophic fibres occupied part of or an entire fascicle (»patchy atrophy»), as in one third of periarteritis nodosa (?) and in one fourth of polymyositis (Fig. 11 B). b) The smallest of the atrophic fibres were localized at the periphery of the fasciculi (Fig. 11 C), as in one third of adult dermatomyositis and of juvenile poly- and dermatomyositis.

iii) *Structure of muscle fibres* a) Cross-striation. Large areas of necrotic muscle fibres were rare, being seen in only a few patients with poly- and dermatomyositis. Solitary necrotic fibres occurred in half the muscles of patients with polymyositis and with juvenile poly- and dermatomyositis. The cross-striation was normal in polymyalgia rheumatica. b) Vacuolisation was seen only in 1 patient with systemic lupus erythematosus and in a few patients of the other groups.

iv) *Number and sites of nuclei* Internal nuclei in more than 5 % of the muscle fibres occurred frequently in patients with polymyositis. More than 8 subsarcolemmal nuclei per fibre in many fibres were found in 14 % of the biopsies from patients with polymyositis and in 2 of the 5 biopsies from juvenile poly- and dermatomyositis.

v) *Interstitial tissue* Proliferation of endomysial connective tissue was found in nearly half the biopsies from patients with polymyositis and scleroderma. Proliferation of endomysial fat was rare: it occurred in systemic lupus erythematosus in 20 of the patients and in the other groups in at most 10 %.

vi) *Blood vessels*. Severe changes were rare and fibrinoid necrosis of the media was virtually absent. Fibrinous proliferation of the intima associated with a narrowed lumen or perivascular proliferation of connective tissue with newly formed capillaries was observed in six biopsies (Fig. 12).

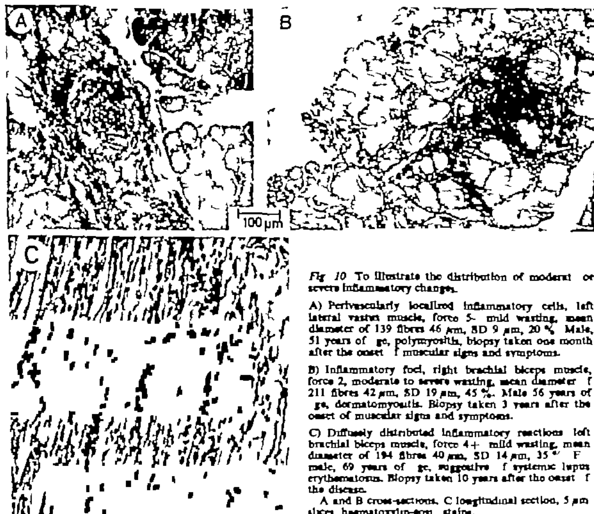


Fig 10 To illustrate the distribution of moderate or severe inflammatory changes.

A) Perivascularly localized inflammatory cells, left lateral vastus muscle, force 5- mild wasting, mean diameter of 139 fibres 46 µm, SD 9 µm, 20 %. Male, 51 years of age, polymyositis, biopsy taken one month after the onset of muscular signs and symptoms.

B) Inflammatory foci, right brachial biceps muscle, force 2, moderate to severe wasting, mean diameter of 211 fibres 42 µm, SD 19 µm, 45 %. Male 56 years of age, dermatomyositis. Biopsy taken 3 years after the onset of muscular signs and symptoms.

C) Diffusely distributed inflammatory reactions left brachial biceps muscle, force 4+ mild wasting, mean diameter of 194 fibres 40 µm, SD 14 µm, 35 %. Female, 69 years of age, suggestive of systemic lupus erythematosus. Biopsy taken 10 years after the onset of the disease.

A and B cross-sections, C longitudinal section, 5 µm slices, haematoxylin-eosin stains.

D) ELECTROMYOGRAPHIC AND BIOPSY FINDINGS AFTER TREATMENT WITH STEROID AND CHLOROQUINE

The incidence and degree of electromyographic changes were the same in the 34 patients who received steroid treatment before the electromyographic examination as in the 76 patients who were not treated by steroids. 20 of 102 patients were treated by steroids (hydrocortison or prednison) before the first biopsy (Table 9). Steroids had been administered for 2 weeks to 6 years (mean 260 days).

In systemic lupus erythematosus the time of treatment varied from 5 to 72 months with a mean duration of 30 months. The drug was with few exceptions either hydrocortison or prednison, when given over a longer time the usual dose was 10—40 mg/day. Of 21 patients in whom histograms of diameters were obtained, 11 patients had not received steroid treatment and tended to have an

Table 9 Steroid treatment more than two weeks before the first examination.

(The figures denote the number of patients)

Disease	EMG total	EMG treat	Biopsy total	Biopsy treat.
Polymyositis	21	3	1	2
Dermatomyositis	15	4	15	
Juven poly-dermat	7	1	5	1
Syst lupus eryth	[illegible]	16	24	11
Syst lupus eryth (*)	7	3	7	
Periarteritis nod (*)	10	5	10	
Syst scleroderma	11		10	0
Local scleroderma	3	0	2	0
Polymyalgia rheum	8	0	8	0

(*) Suggestive but not diagnostic



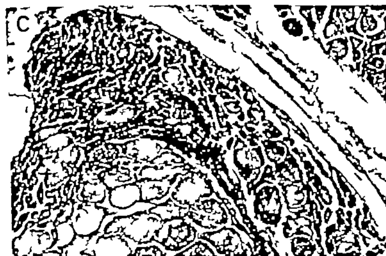


Fig 11 T illustrat the different types of distribution of trophic fibres.
A) Randomly distributed, right deltoid muscle, force 1 severe wasting, mean diameter f 219 fibres 42 μm, SD 12 μm, 28 % Female 47 years of ge, polymyositis associated with rec tal cancer Biopsy t ken 1 1/2 years after the onset of muscular signs and symptoms.
B) »Patchy atrophy» brachial biceps muscl moderately decreased force and wasting, mea diameter of 237 fibres 34 μm SD 13 μm, 39 % Mal 58 years of age, periarteritis nodosa(?) Specimen taken at autopsy 7 years after the onset of muscular signs and symptoms.
C) The smallest atrophic fibres localized at the periphery of the fascicle, right lateral vastus, force 5- no wasting, mean diameter f 249 muscle fibres 38 μm, SD 17 μm, 45 % Female 14 years of age polymyositis. Biopsy taken 3 months after the onset of muscular signs d ympt ms.
Cross-sections, 5 μm slices, haema toxylin-eosin stains.

Fig 12 T Illustrate fibrinous prolif ration f the intima associated with a narrowed l men and perivascular proliferation of the connective tissue with newly formed capillaries (arrow). Right anterior tibial muscle, f rce 5- mild wasting, mean diameter of 196 fibres 56 μm, SD 12 μm 22 %
Female, 29 years ld, systemic lupus erythematosus. Biopsy taken 11 years fter the onset of the disease. Electromyography in the contralateral muscle showed signs of myopathy Cross-section, 5 μm slice, haemat xylin-eosin stain.

average diameter slightly above normal (+23 %) whereas the diameter in 10 patients who had received steroid treatment was normal (+10 %). In the other biopsies neither the quantitative nor the qualitative estimation differed in patients with and without steroid treatment.

7 of 28 patients with systemic lupus erythematosus were treated with chloroquine: neither electromyographic nor histopathological findings differed from findings in untreated patients. Vacuoles assumed to be characteristic of chloroquine myopathy (Eadie and Ferrier 1966) were absent in the biopsies of these patients.

E) CORRELATIONS

An attempt was made to correlate electromyographic abnormalities (duration and amplitude of motor unit potentials, incidence of polyphasic potentials, pattern and amplitude during full effort, and incidence of spontaneous activity) and histopathological abnormalities including abnormalities in the distribution of fibre diameters to the duration of disease, the sedimentation rate, to the findings in the electrophoretic pattern of serum proteins and to serum enzymes (creatine phosphokinase and lactate dehydrogenase).

There was no relation between the duration of the disease, the most frequent laboratory findings (sedimentation rate, changes in fractions of serum protein), and electromyographic and histopathological abnormalities.

The only positive correlations are listed below

i) *Duration of motor unit potentials and histopathological findings*

Randomly distributed loss or block of fibres results in a decrease in duration of motor unit potentials. All patients with polymyositis and dermatomyositis had a significant decrease in duration and most biopsies showed the expected scattered loss of muscle fibres and fibres with cloudy cross-striations in addition to inflammatory changes. In systemic lupus erythematosus the decrease in duration of motor unit potentials was less when there was no evidence of fibre loss than when there was fibre loss. However the duration did not decrease proportionally with the fibre loss.

ii) *Incidence of polyphasic potentials and histopathological findings*

Polyphasic potentials in myopathy are assumed to be due to loss of fibres in the vicinity of the recording electrode such that potentials of surviving fibres at a distance of 0.5–1 mm from the electrode appear as separate spikes rather than as mere irregularities (Buchthal and Rosenfalck 1963). In accordance with this interpretation, many degenerated muscle fibres in a biopsy were associated with a high incidence of polyphasic potentials. Also an increase in the spread of diameters in μm and in per cent was related to an increased incidence of polyphasic potentials (polymyositis, $P<0.001$).

iii) *Spontaneous activity as related to*

a) *histopathological findings*. The incidence of spontaneous activity was the electromyographic abnormality most closely related to the severity of histopathological changes. Thus in 11 patients with polymyositis who had spontaneous activity abnormalities (qualitative and quantitative) in the biopsy were more severe than in the 10 patients who had no spontaneous activity: 5 of the patients whose biopsies contained large fields of atrophic fibres had spontaneous activity (see p. 22).

An exception was systemic lupus erythematosus, of 5 patients with spontaneous activity 3 had a normal or near-normal biopsy

b) *other electromyographic parameters*. The patients who had spontaneous activity also had the lowest amplitude of the interference pattern and the highest incidence of polyphasic potentials.

c) *serum enzymes*. Of the 8 patients with polymyositis who had increased activity of serum creatine phosphokinase, lactate dehydrogenase or both (p. 12), 7 had spontaneous activity

iv) *Weakness and wasting in relation to electromyographic findings*. In polymyositis and dermatomyositis the decrease in mean duration of motor unit potentials was largest in muscles which were wasted. On the other hand, in half the patients with systemic lupus erythematosus electromyographic changes were not associated with weakness or wasting of or pain in the muscles. In periarteritis nodosa(?) and in polymyalgia rheumatica all patients had pain, tenderness, weakness or wasting and two thirds of the patients had electromyographic abnormalities compatible with myopathy irrespective of the severity of clinical signs and symptoms.

v) *Weakness and wasting in relation to the incidence of atrophic fibres*. When weakness and wasting were absent there was no increased incidence of atrophic fibres. Conversely, when there was weakness and wasting there was as often an increased incidence of atrophic fibres as not.

DISCUSSION

A) CLASSIFICATION

In agreement with previous studies the classification of collagen diseases was based on a combination of clinical and laboratory findings. In this way about 90 % of the patients could be classified.

The first description of inflammatory disease of muscle associated with skin involvement was given by Wagner (1863) who introduced the term *polymyositis* later replaced by *dermatomyositis* (Unverricht 1887). A case of inflammatory myopathy without skin involvement was reported by Hepp (1887). Few years later Steiner (1901–1905) reviewed the 28 cases known at that time and defined dermatomyositis as: »An acute, subacute or chronic disease of unknown origin characterized by oedema, dermatitis and muscle inflammation». A complete bibliography up to 1940 of later cases was given by Kinney and Maher (1940). In the 1950's the disease received new attention (Adams et al. 1953, Eaton 1954, Garcin et al. 1955 b, van Bogaert et al. 1955, Christianson et al. 1956, Coërs 1956, Walton and Adams 1958). Based on clinical findings Walton and Adams (1958) divided the disease into four groups: I. Polymyositis with clinical evidence suggesting a purely muscular affection (acute, subacute or chronic in childhood, in early adult life, in middle or late life). II. Polymyositis with some skin manifestations or with some features of associated »collagen« disorder. III. Florid dermatomyositis or severe collagen disease with less striking muscular manifestations. IV. »Carcinomatous myopathy» and dermatomyositis or polymyositis in association with malignant disease. This classification was adopted by Barwick and Walton (1963) and slightly modified by Pearson (1966) who included polymyositis in conjunction with Sjögren's syndrome. Denny Brown (1960) distinguished 4 different types of histopathological changes not identical with the clinical subgroups of Walton and Adams (1958). (I. Polymyositis, II. Necrotizing myopathy, III. Vacuolar myopathy and IV. Granular degeneration).

The special clinical and histopathological features of dermatomyositis in childhood have been described by Banker and Victor (1966). They drew attention to the changes in small blood vessels with infiltration of inflammatory cells, proliferation of intima, occlusion by fibrin thrombi and subsequent infarction of tissue. They also emphasized that tissues other than skin and muscle are consistently affected and that the fundamental pathological change is an angiopathy.

The disease has recently been reviewed by Rose and Walton (1966), Diessner et al. (1966) and Winkelmann et al. (1968).

The present study comprises 43 patients with *polymyositis and dermatomyositis*, 7 of whom were children. The adult patients with polymyositis and dermatomyositis were classified separately for the following reasons. In adult patients with dermatomyositis females were affected 3 times as often as males. In polymyositis the incidence was the same in both sexes. Weakness of the limbs was somewhat more pronounced in polymyositis than in dermatomyositis. Similarly the force of flexion of the neck was decreased in 57 % of patients with polymyositis compared to 33 % with dermatomyositis, and dysphagia tended to be more frequent in polymyositis (44 %) than in dermatomyositis (33 %).

The type and degree of electromyographic changes in polymyositis and dermatomyositis were the same except for the incidence of spontaneous activity which occurred in half the patients with polymyositis as against a third with dermatomyositis. With the exception of focal inflammatory changes, abnormalities in the muscle biopsy were more pronounced in polymyositis than in dermatomyositis. Abnormal spread of diameters (>30 %) occurred in half the patients with polymyositis as compared to a third with dermatomyositis. Two thirds of the patients with polymyositis showed necrotic changes of the muscle fibres as compared to one third of the patients with dermatomyositis. On the other hand,

interstitial focal inflammatory changes dominated the biopsies of patients with dermatomyositis.

Systemic lupus erythematosus was first described and distinguished from the cutaneous form by Kaposi (1872). Osler (1895 1903) emphasized the visceral complications as well as the tendency to remissions and exacerbations. The description of the pathology of the disease begins with the report of Libman and Sacks (1924), followed by the more detailed analysis of Baehr Klemperer and Schifrin (1935) and Klemperer et al. (1941), which includes the histopathological findings in muscle LE-cells as typical of the disease were discovered by Hargraves et al. (1948). Harvey et al (1954) presented the first complete review Recently the literature and findings in 520 patients were reviewed by Dubois (1966).

The present study comprises 28 consecutive patients with clinical and laboratory signs typical of systemic lupus erythematosus. The occurrence of LE-cells alone is not sufficient for classification because up to 20 / of patients with rheumatoid arthritis (Klevits et al. 1956, Sigler et al. 1958 Fallet et al. 1959 Miescher et al. 1966) and occasionally with other diseases may show typical LE-cells on repeated investigations although the patients in question did not have the involvement of the other organ systems usually affected in systemic lupus erythematosus. Therefore patients with arthritis were only classified as systemic lupus erythematosus when rheuma-serology was negative or when t least 2 organ systems other than joints were involved. In this study 3 patients with typical LE-cells on more than one investigation were excluded on this basis.

The first description of clinical and pathological findings in *periarteritis nodosa* is that by Kussmaul and Maier (1866). The pathological changes in the arteries were described by Arkin (1930), Zeek et al. (1948) Zeek (1952) Moskowitz (1960) Sokoloff (1963) and Alarcón-Segovia and Brown (1964) Muscular changes are less prominent than in other types of collagen diseases (Wallace et al. 1958 Pearson 1964 Camp and Engel 1965) but necrotizing angiitis in the muscle biopsy has been reported in about 35 % of 53 patients with proven periarteritis nodosa (Maxeiner et al. 1952, Wallace et al. 1958).

Mononeuritis multiplex or polyneuritis is the most frequent neuromuscular complication. It occurred in half of 29 cases confirmed by necropsy (Lovshin and Kernohan 1948).

Ten patients in this study were classified as probably periarteritis nodosa. Clinical and laboratory findings were compatible with this disease (p. 16) or with hypersensitive angiitis (Alarcón-Segovia and Brown 1964 Anonymous in Arthr and Rheum. 1970.) However neither biopsy (of muscle kidney liver skin, cerebral cortex) nor autopsy (4 patients) revealed the typical necrosis of the medial layer of arteries. This may have been due to the fact that the arterial lesions are segmental and may be missed in small samples of tissue (Sokoloff 1961 Gardner 1965 Frohnert and Sheps 1967)

The first detailed description of systemic *scleroderma* is by Carlo Curzio in 1753 (Curzio 1755 Rodnan and Benedek 1962) the term »scleroderma» was introduced by Gintrac in 1847 Local scleroderma in the form of hemiatrophy was described first by Parry (1825) and Romberg (1846) In recent reports the disease has been divided into several subgroups but opinions differ as to the criteria for these subdivisions (Tuffanelli and Winkelman 1961 Sackner 1966, Korting and Holzmann 1967 Winkelman 1971).

Histological evidence of muscular involvement was described by Westphal (1876), Méry (1889), Dinkler (1891) and Lewin and Heller (1895).

Histopathological abnormalities in muscles occur in about half the patients examined (Rodnan and Medsger 1966, Medsger et al. 1968, Bekény 1970). There is however disagreement as to the incidence of inflammatory changes: Winkelman (1971) found it minimal or absent, Medsger et al. (1968) considered it the most important finding next to interstitial fibrosis.

The classification of the 14 patients with scleroderma was based on the typical skin lesions.

Polymyalgia rheumatica described by Bruce (1888) as »senile rheumatic gout» was rediscovered by Meulengracht and coworkers (Meulengracht 1945 Holst and Johansen 1945 Meulengracht and Schwartz 1952). The term »polymyalgia rheumatica» was introduced by Barber (1957). Pain in proximal muscles, increased sedimentation rate, negative rheuma-serology normal or near-normal muscle biopsy and response to steroid therapy are the main features of the disease, which has recently been reviewed by Vischer et al. (1969), Kaiser (1969) and Hunder et al. (1969).

Giant-cell arteritis is present in about one third of patients with polymyalgia rheumatica (Dixon 1969). There was no definite difference either in symptoms or in clinical and laboratory findings, when the polymyalgia rheumatica was complicated by temporal arteritis and when it was not (Kogstad 1965).

The 8 patients of this study had widespread muscular pain restricting movement especially in the shoulder and hip girdle increased sedimentation rate negative rheuma-serology and immediate response to steroid treatment or spontaneous recovery within 1 or 2 years. Only 1 patient (case report 7

p 40) in this study had temporal arteritis confirmed by biopsy

Most workers agree that muscle biopsy in poly myalgia rheumatica is usually normal (Boyle and Beatty 1961 Andrews 1965 Vischer et al. 1969) or nearly normal (Gordon et al. 1964 Kaiser 1969). However quantitation revealed abnormalities in 4 of the 6 patients in whom the biopsy was suitable for measurements.

B) ELECTROMYOGRAPHIC FINDINGS

Of the 110 patients examined in this study 85 % showed electrophysiological evidence compatible with myopathy This is a high percentage of muscular involvement considering that some patients with collagen diseases have no clinical evidence of neuromuscular involvement. In part this high incidence of myopathic changes is due to selection of the patients because they were referred on account of muscular weakness, wasting and pain On the other hand patients with systemic lupus erythematosus were referred consecutively and also in this group 82 % had electrophysiological changes consistent with myopathy Of these only 52 (12/23) had clinical findings suggestive of myopathy

An electromyographic examination can more easily be obtained in several muscles than a biopsy In 80 % of the patients electromyography of one muscle (usually proximal) sufficed to demonstrate the manifestations of a myopathy In the remaining 19 patients evidence of myopathy was first revealed when electromyography was performed in an additional muscle.

The first electromyographic reports on *polymyositis* and *dermatomyositis* were 2 short notes on findings in dermatomyositis (Guy et al. 1950 Lambert et al. 1950). Lambert et al. (1950) drew attention to spontaneous activity the decrease of duration and amplitude of motor unit potentials as well as a high incidence of polyphasic potentials. In a series of 80 patients Lambert et al. (1954) and O'Leary et al. (1955) described spontaneous activity as the most prominent electrophysiological feature more frequently seen without than with cutaneous lesions. Buchthal and Pinelli in 11 patients (1952, 1953), later supplemented by findings in 14 patients (Buchthal and Rosenfalck 1963), found 30—50 % decrease in average duration of the motor unit potentials, a . to 7-fold increase in the incidence of polyphasic potentials, spontaneous activity of short duration in one third of the patients, the same incidence as reported by Richardson (1956).

The interpretation of spontaneous activity in myopathy is still a matter of discussion. Some assume it to be due to destruction of distal branches of motor nerves (Richardson 1956), others (Buchthal and Rosenfalck 1966) to the decrease in intracellular potassium to half normal or less (Bladh et al. 1953 Horvath et al. 1955).

All 43 patients examined in this study had a significant decrease in mean duration of motor unit potentials. Increased incidence of polyphasic potentials was seen in 65 % of the patients and when present it occurred often with a higher incidence than in other types of collagen diseases. Fibrillation potentials or positive sharp waves were seen in half the muscles in polymyositis and in a third of the muscles in dermatomyositis. »Pseudomyotonic» bursts were found in 15—20 of the patients, an incidence 3 to 4 times greater than reported in 13 patients (Hausmanowa-Petrusewicz and Jedrzejowska 1971).

Electromyographic changes in *systemic lupus erythematosus* similar to those in polymyositis have been described by Degos et al. (1949) in 1 patient, by O'Leary et al. (1955) in 2 patients. The first quantitative study is that by Erbslöh and Baedeker (1962): they found evidence of myopathy in 14 of 15 patients.

Of the 28 patients in this study 23 had electromyographic findings indicative of myopathy (82 %). 11 patients with clearcut electromyographic abnormalities had no clinical signs or symptoms of muscular involvement.

Electrophysiological studies in *periarteritis nodosa* showed slowed motor conduction (Lovelace 1964) and signs of myopathy when there was histological evidence of an inflammatory myopathy (Garcin et al. 1955 a, Erbslöh and Eisenburg 1963)

All 10 patients in this study referred for electromyographic study had signs and symptoms of muscular involvement but not of neuropathy Electromyography showed signs compatible with myopathy in 7 patients. Some of these patients developed neuropathy later

O'Leary et al. (1955) found electromyographic changes in about half of the patients with *scleroderma* similar to those in polymyositis. In a quantitative study Hausmanowa-Petrusewicz and Kozminska (1961) reported a decrease in duration of motor unit potentials in 19 of 25 muscles from 14 patients with generalized scleroderma and in muscles subjacent to the skin lesions in 11 of 12 patients with localized scleroderma. Similar Bekény (1970) found evidence of myopathy in 75 % of 33 patients. It is not stated whether his findings are based on quantitative or on qualitative observations. 17 of 19 patients without weakness or wasting had either electromyographic or histopathological abnormalities or both. Thompson et al. (1969) found a much lower incidence of electromyographic abnormalities (4 of 15 patients).

Half of the 11 patients with systemic scleroderma in this study had evidence of a decreased mean

duration of motor unit potentials compatible with myopathy

The literature concerning electromyographic findings in *polymyalgia rheumatica* is confusing. Vischer et al. (1969) found evidence of myopathy in all 8 of their patients, as I did in 6 of my patients. American workers (reviewed by Healy et al. 1971) consider that a normal electromyogram is prerequisite to the diagnosis of polymyalgia rheumatica. The divergence cannot be explained by steroid treatment and is due rather to the fact that absence of »myopathic« changes were estimated from observation of potentials on the screen of the oscilloscope and not by quantitative determination of the duration of motor unit potentials.

Clinical, histopathological and electromyographic evidence of muscular involvement was found in only 4 of 40 patients with *Sjögren's syndrome* by Bunim (1961). In 19 of the patients without clinical evidence of myopathy muscle biopsy showed moderate to severe inflammatory changes in 3 and mild changes in 11. Electromyographic studies were not performed in patients without clinical evidence of muscle involvement. Myopathy confirmed by electromyographic and histopathological findings, has been reported by Silberberg and Drachman (1962) in 4 patients, by Fox in 1 case (1966) and by Brown et al. (1968) in 3 cases with myasthenic features.

One of my patients with Sjögren's syndrome had signs and symptoms of scleroderma and another of systemic lupus erythematosus. Both had electromyographic and histopathological evidence of muscle involvement, both without clinical signs and symptoms.

C) HISTOPATHOLOGICAL FINDINGS

The histopathological investigation is confined to a small area of the muscle which need not be representative of overall abnormalities. In 15 patients biopsies were taken in different proximal muscles at short time intervals. In 10 the second biopsy showed the same degree of abnormality as the first, in 4 the second biopsy was more abnormal and in 1 the findings were less severe than in the first biopsy.

The mean of the orthogonal major and minor diameters was used as a measure of cross-sectional area because there was agreement with the area determined by planimetric measurement (Song et al. 1963, Buchthal and Rosenfalck unpublished). Data in the literature on muscle fibre diameter are scarce and vary. The values given by Schwalbe and Mayeda (1890), Coërs and Hildebrand (1965) and Rebeiz (1970) are within the range of normal muscles given in Fig. 1, the variation in mean diameter from muscle to muscle being less than reported by Sissons (1963). The average diameters reported by Reske-Nielsen et al. (1970) in m. palmaris longus were 10–20 μm larger.

Biopsies in which there was doubt as to whether there were signs of myogenic or neurogenic impairment. The biopsy of 5 patients with polymyositis showed fields of 20–50 atrophic fibres often with preserved cross-striations. These fields are often considered to indicate a neurogenic lesion even in biopsies which otherwise indicate myopathic impairment (Greenfield et al. 1957) and in patients without clinical evidence of neuropathy (Camp and Engel 1965). If neurogenic in origin, one must assume either denervation of intermingling fibres of several motor units or reinnervation in the same motor unit by peripheral sprouting. Since there was no electrophysiological evidence of loss of motor units or regeneration and since these biopsies otherwise showed changes typical of inflammatory myopathy, the question arises whether local impairment of blood supply can account for the fields of atrophic fibres. A similar mechanism has been suggested (Engel 1970) to explain the occurrence of small fibres in the periphery of the fasciculi (Banker 1962). In the present study this aggregation of small fibres was seen in 6 patients with dermatomyositis, in 2 with juvenile poly- and dermatomyositis and in 1 with systemic lupus erythematosus and 1 with scleroderma. Vascular changes are known to occur in muscles of patients with collagen diseases (*light microscopy*: Adams et al. 1953, Garcin et al. 1955 b, Boylan and Sokoloff 1960, Banker 1962, Sokoloff 1963, Banker and Victor 1966, Delbarre et al. 1968; *electron microscopy*: Müller and Waldmann 1967, Norton et al. 1968, Norton 1970). Hypoxia has also been demonstrated by measurement of the local intramuscular oxygen tension (Kunze 1970). Moreover, myopathic changes have been produced in rabbits by microarterial embolization (Hathaway et al. 1970). The changes in blood proteins, common in collagen diseases, are assumed to affect the microcirculation (Ditzel 1959, Wells 1964). Tomlinson et al. (1969) have found areas of atrophic fibres mostly in the lower extremities in bed-ridden patients with dementia, prolonged coma after head injury and other chronic diseases with general wasting and without evidence of lower motor neuron lesions. This may be due to a chronic decrease in blood flow.

D) ELECTROMYOGRAPHY AND HISTOPATHOLOGY OF MUSCLE AS DIAGNOSTIC AIDS

Neither electromyographic nor histopathological findings in the muscles are specific for any one of the collagen diseases. The divergence between histopathological and electrophysiological findings was particularly evident when abnormalities in the biopsy

were slight or negligible and the mean duration of motor unit potentials was decreased. 6 patients without abnormalities in the biopsy had electromyographic changes compatible with myopathy (1 with dermatomyositis, 2 with systemic lupus erythematosus, 1 with systemic scleroderma and 2 suggestive of periarteritis nodosa). The same was the case in 15 of 18 patients with systemic lupus erythematosus, in whom biopsy changes were slight and in 6 of 8 patients with polymyalgia rheumatica, in whom the biopsies were either normal (3) or showed only slight abnormalities. Conversely only 1 patient with systemic lupus erythematosus who had histopathological evidence of an inflammatory myopathy had normal findings on electromyography »Vacuolar myopathy« though rare, has been thought to be specific for systemic lupus erythematosus (Pearson and Yamazaki 1958) In my material vacuoles occurred somewhat more often in polymyositis and dermatomyositis.

Although abnormalities in the biopsy and in the electromyogram do not establish a diagnosis, they assist in distinguishing myogenic impairment in collagen diseases from neurogenic: the biopsy was indicative of myopathy in 40 and the electromyogram in 85 of the patients. The degree of abnormalities may help to distinguish between different types of collagen disease: severe inflammatory changes associated with severe electromyographic abnormalities including spontaneous activity and a high incidence of polyphasic potentials are more apt to occur in polymyositis and dermatomyositis than in the other forms of collagen disease. A normal or slightly abnormal biopsy associated with pronounced electromyographic changes, but with fewer polyphasic potentials and often without spontaneous activity speaks in favour of systemic lupus erythematosus or polymyalgia rheumatica. A similar discrepancy between a pronounced decrease in the duration of motor unit potentials and histopathology was found in thyrotoxic myopathy (Yates 1963 Ramsay 1965) and was explained by a transient block of muscle fibres (Buchthal 1970), since clinical improvement was associated with normalization of the duration of motor unit potentials (Yates 1963 Ramsay 1965).

E) COLLAGEN DISEASES AS A CLINICAL ENTITY

Even if the original concept of collagen diseases was based on a wrong assumption (p. 8) there are reasons to distinguish them clinically until the aetiology is known. The concept of collagen diseases is somewhat unclear The four diseases (systemic lupus erythematosus, periarteritis nodosa, scleroderma and poly and dermatomyositis) accepted as collagen diseases by the American Rheumatism Association (Copeman 1969) do not form an entity distinct from other rheumatic diseases. The clinical picture immunological phenomena and histopathological findings of systemic lupus erythematosus, for example resembles rheumatoid arthritis more than systemic scleroderma. Polymyalgia rheumatica resembles the four »original collagen diseases« as much as they resemble each other At the onset polymyalgia rheumatica can be clinically indistinguishable from polymyositis. Many patients with polymyalgia rheumatica develop rheumatoid arthritis or other related diseases at a later time (Hunder et al. 1969). About one third of patients with polymyalgia rheumatica go on to develop symptoms and signs of giant-cell arteritis sooner or later (Dixon 1969). General arteritis has been reported in some cases (Hamrin et al. 1964 1965). Changes in blood vessels are a common and generally accepted feature in collagen diseases (Sokoloff 1963).

Still there are some interesting reports on the relation of polymyalgia rheumatica to rheumatoid arthritis. Waaler and Milde (1968) found a patient with typical polymyalgia rheumatica, typical also in that the patient had negative rheuma tests in the serum, who had not only giant-cell arteritis but also rheumatoid granuloma with rheumatoid factor in the biopsy of the temporal artery Rheumatoid factor in »sick tissue« (synovial membranes and rheumatoid nodules) has been demonstrated as well in rheumatoid arthritis with and without rheumatoid factor in the serum (Milde and Tönder 1968).

This study confirms the close relationship between these diseases. As to histopathological findings in skeletal muscle they are common in all except polymyalgia rheumatica. Electromyographic abnormalities compatible with myopathy varied in this study from 57 % to 100 %, being least frequent in scleroderma and most frequent in poly- and dermatomyositis. Because the patients with systemic lupus erythematosus were the only ones referred consecutively the incidence of myopathy in the other groups has to be taken with reservation. In rheumatoid arthritis, myopathic changes were found in 55 % and unspecific electromyographic abnormalities in 23 % (Moritz 1963). Finally it has to be emphasized that these overlapping histopathological and electromyographic abnormalities are not specific to the collagen diseases in general, nor to any one of them separately

F) COLLAGEN DISEASES AND MALIGNANT DISEASE

Stertz (1916) was the first to report a case of dermatomyositis with cancer

Of the 31 patients with polymyositis and dermato-

myositis above 40 years of age, 5 had carcinoma 1 had a benign thymoma. The incidence of malignancy (16 %) was thus similar to that found by Mills (1963), Pearson (1966) and Winkelman et al. (1968), and less than reported by Arundell et al. (1960) and Shy (1962). In addition, 1 of the 28 patients with systemic lupus erythematosus had acute myeloid leukaemia.

G) DIFFERENTIAL DIAGNOSIS

i) *Steroid myopathy* Patients with collagen diseases are often treated by steroids and when there is muscle involvement the question may arise whether this is due to the primary disease or secondary to steroid treatment.

Steroid myopathy can neither clinically nor electrophysiologically be distinguished from myopathy associated with collagen diseases (Hagström et al. 1961, Kaeser and Kocher 1970)

In 6 patients with Cushing's syndrome Müller and Kugelberg (1959) found electromyographic evidence of myopathy whereas Pleasure et al (1970) found normal conditions in 1 patient.

In the present series steroid myopathy as a cause of the electromyographic abnormalities was probably of subordinate importance The incidence and degree of abnormalities was the same whether the patients were treated or not, and clinical signs and symptoms of muscle impairment in polymyositis and dermatomyositis were found before treatment.

As to histopathological findings in steroid myopathy there is agreement in the literature that inflammatory changes are absent (Hagström et al. 1961 Ellis 1956, Afifi et al. 1968 Afifi and Bergman 1969 Kaeser and Kocher 1970 Pleasure et al. 1970). There is disagreement as to whether there are degenerative changes in addition to atrophy or whether there is only atrophy (Faludi et al. 1966, Pleasure et al. 1970)

ii) *Sarcoidosis* Muscular sarcoidosis may be clinically and electrophysiologically indistinguishable from polymyositis, systemic lupus erythematosus and periarteritis nodosa unless the biopsy contains epithelioid granulomas (Hinterbuchner and Hinterbuchner 1964) Electromyography shows evidence of myopathy in most cases reported in the literature (Hinterbuchner and Hinterbuchner 1964).

iii) *Thyrotoxic myopathy* Since the basal metabolic rate is often increased in polymyositis (Eaton 1954 Diessner et al. 1966), polymyositis has to be differentiated from thyrotoxic myopathy This usually presents no difficulty because other tests of thyroid function are normal and the muscle biopsy shows severe changes in polymyositis which are absent in thyrotoxic myopathy Moreover fibrillation potentials, present in half the patients with polymyositis, were absent in thyrotoxic myopathy (Ramsay 1965 Buchthal 1970).

iv) When there are no other members of the family affected the differentiation of *progressive muscular dystrophy* from subacute and chronic polymyositis may present difficulties. The clinical and histopathological differences have been emphasized in numerous series (Rowland 1958 Pearson and Rose 1960, Barwick and Walton 1963 Pearson 1966 Rose and Walton 1966, Thompson 1968 Korten et al. 1970). Electromyographic changes are the same except that spontaneous activity seen in half the patients with polymyositis, occurred in about one third of the patients with muscular dystrophy (Buchthal 1965).

SUMMARY

Clinical, electromyographic and histopathological findings have been studied in 110 patients with collagen diseases: polymyositis, dermatomyositis, systemic lupus erythematosus, scleroderma, polymyalgia rheumatica and patients with clinical signs and symptoms of periarteritis nodosa.

Patients with systemic lupus erythematosus were examined consecutively regardless of clinical signs and symptoms of neuromuscular involvement. The other patients were referred for electromyographic examination because of muscular weakness, wasting, pain or tenderness.

The electromyographic studies were analyzed quantitatively by measuring duration and amplitude of motor unit potentials, incidence of polyphasic potentials and spontaneous activity and the pattern and amplitude of motor unit potentials during full effort. The muscle biopsies were evaluated qualitatively by the criteria of Greenfield et al. (1957). There were also examined quantitatively with respect to the mean diameter spread of diameter and the incidence of atrophic and hypertrophic fibres.

Electromyographic findings compatible with myopathy were found in 85 % including 14 of 17 patients in whom there were no clinical signs or symptoms of muscle involvement.

Among the different groups of collagen disease examined, only patients with polymyositis and dermatomyositis showed a close relation between the degree of clinical involvement and electromyographic and histopathological abnormalities.

Of the 24 patients with systemic lupus erythematosus in whom a biopsy was taken histopathological changes were slight or absent in most (17). On the other hand nearly all patients showed electromyographic abnormalities compatible with myopathy. The same was found in polymyalgia rheumatica.

Two thirds of the patients with clinical and laboratory findings suggestive of periarteritis nodosa and of the patients with scleroderma showed electromyographic evidence of myopathy. The muscle biopsy was clearly abnormal only in one third.

Neither the electromyographic nor the histopathological changes are specific for a given type of collagen disease. Severe inflammatory changes are, however associated with severe electromyographic abnormalities and they are more apt to occur in polymyositis and dermatomyositis, whereas a normal or slightly abnormal biopsy associated with pronounced electromyographic changes speaks in favour of systemic lupus erythematosus or polymyalgia rheumatica.

In 9 patients there was doubt as to whether the biopsy indicated myogenic or neurogenic impairment in spite of clinical and electromyographic evidence of myopathy. 5 of these patients were diagnosed clinically as polymyositis. The biopsy showed large fields of atrophic fibres in addition to abnormalities which often are seen in myopathy. It is suggested that the large fields of atrophic fibres of these patients are due to local insufficiency of blood supply rather than to reinnervation after denervation.

1) **Polymyositis.** Patient 438 39-year-old electrician, without family history of neuromuscular disease. For 1 year he had noticed slowly progressive fatigue and loss of weight (20 kg). There were intermittent weakness and tenderness of the muscles of the shoulder girdle, diplopia and dysphagia (free intervals of 1 month). Dry eczema in the palms was the only sign of skin involvement.

Neurological examination 6 months after the onset of the disease showed wasting and weakness in the muscles of the shoulder girdle and the upper arms. The force of flexion of the neck was diminished (4-) extension of neck was normal. Tendon jerks were normal.

Laboratory findings. Latex fixation test was positive. Creatine/creatinine excretion was increased (40 % per day: normal 6 %). The sedimentation rate, blood count, haemoglobin, blood sugar serum creatinine, total serum protein and electrophoresis were normal. LE cells were absent, basal metabolic rate was 26—30 % above normal, other tests of thyroid function were normal. Search for malignancy was unrevealing. Serum creatine phosphokinase and lactate dehydrogenase were not examined.

Electromyography (1 year after the onset of the disease). In the left deltoid muscle (force 3+) the mean duration and amplitude of motor unit potentials were normal. The incidence of polyphasic potentials was 32 % (normal < 12 %) and there was profuse fibrillation. In the right brachial biceps muscle (force 3+) the mean duration of motor unit potentials was decreased by 35 % and their amplitude by 46 %. There was neither polyphasia nor spontaneous activity. Both muscles showed an interference pattern of normal amplitude during full effort.

Biopsies. In the first biopsy obtained from the right deltoid muscle 4 months after the onset of the disease the average diameter of muscle fibres was decreased by 37 % and was normal in the second biopsy 2 years and 3 months later. Both biopsies showed marked increase in scatter of diameter in per cent (38 and 32 %) and only the second in μm (28 μm). The atrophic fibres occurred in patches in the first and were randomly distributed in the second biopsy. Both biopsies contained perivascular and interstitial focal areas as well diffusely distributed inflammatory cells.

On steroid therapy for 2 years he recovered and remained well for 3 1/2 years. Then he relapsed and the right brachial biceps showed the same electromyographic changes as during the first attack.

2) **Dermatomyositis.** (Fig. 13) Patient 509 55-year old housewife without family history of neuromuscular disease. For 4 months she had noticed weakness and tenderness in the muscles of the shoulder girdle and 1 month later in the hip girdle. A few weeks later there was dermatitis of the face, and in the scapular area. She had difficulty in chewing and swallowing and could not raise her head from the pillow. The rectal temperature was 37.5—38°C, she was tired and there was transient intestinal involvement.

Neurological examination. There was wasting and weakness of the proximal muscles, more pronounced in the upper than in the lower extremities. The force of flexion and extension of the neck was markedly decreased. Tendon jerks were absent or weak (knee jerks). There was heliotrope colored rash on the eyelids and erythema, oedema and hyperaemic scaling of the skin of the face and over the scapular area. The skin of the fingers was erythematous and so tight as to cause slight contracture in flexion.

Laboratory findings. The sedimentation rate was 29—47 mm/h (normal 2—10 mm/hour). Total protein, albumin and alpha 1 globulin in the serum were decreased by 23, 35 and 36 % and alpha 2 globulin increased by 46 %. Creatine phosphokinase was slightly increased at the first examination and normal 6 weeks later. Lactate dehydrogenase was increased (5 times normal). Rheuma-serology and LE-cells were negative. Skin biopsy from the left lower thoracic wall showed evidence of chronic scleroderma.

Electromyography. The left brachial biceps muscle (force 4) and the left femoral rectus muscle (force 4-) showed 50—60 % decreased mean duration of motor unit potentials, 20—30 % polyphasic potentials and spontaneous activity at 5—20 sites with pseudomyotonic discharges. The mean amplitude of the individual motor unit potentials and the amplitude and pattern of the response during full effort were normal.

Biopsies from the right brachial biceps and right lateral vastus muscle showed normal spread in per cent, but increased in μm (15 μm) and normal mean diameter of muscle fibres. The cross-striation was lost in small areas and there were vacuoles. The brachial biceps had small foci of inflammatory cells possibly secondary to necrosis of muscle fibres. The lateral vastus muscle had diffuse and perivascularly localized inflammatory cells. Internally localized nuclei occurred more frequently than normal and the number of sarcolemmal nuclei was increased. There was slight proliferation of connective tissue.

Steroid treatment improved the cutaneous involvement and the muscle weakness, except the dysphagia. 3 1/2 months later she had acute attack of abdominal pain. Laparotomy showed carcinomatous tissue occluding the large intestine. She died 10 days later and autopsy showed metastatic adenopapilliform cancer of the right ovary.

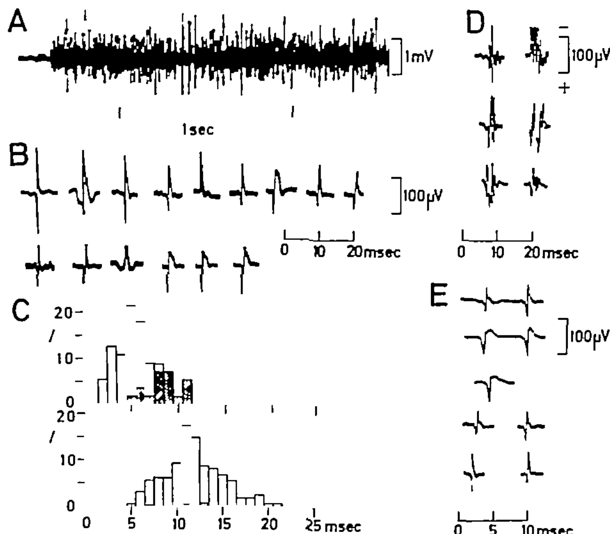


Fig 13 Electromyographic findings in the left brachial biceps (A—E) and histopathological findings in the right brachial biceps muscle (F—G).

Patient 509 with dermatomyositis (case report 2, page 33)

A Interference pattern of diminished amplitude during f ll effort

B Samples f motor unit potentials of simple shape.

C Distribution f the duration of motor unit potentials (bov) the patient (below) 10 norm l subject f the sam ge The shaded columns represent polyphasic potential (29 f all potentials in the patient and 3 in the normal muscles) The mean *duration of ll motor un t potentials in the patient was* 8 5 msec, (SD 2.3 msec, 56 potentials) The mean duration in normal muscle was 11 3 msec (SD 3.2 msec, 161 potential). Th mea mplitude of the randomly recorded moto unit potentials was 330 µV (SD 210 µV) in the patient and 260 µV (SD 120 µV) i normal muscle.

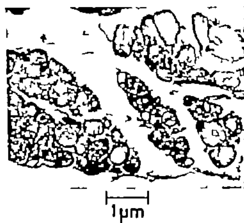
D Samples of polyphasic potentials.

E. Spontaneous discharges (fibrillation potentials and positive sharp waves) were found at 5 sites in the muscle.

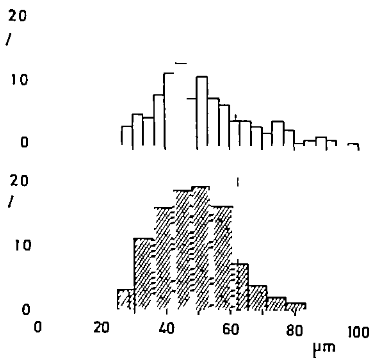
F (left) The longitudinal section shows inflammatory changes and necrotic fibres, (right) the cross-section shows randomly distributed atrophic fibres and vacuoles. Haematoxylin-eosin stains, 5 µm slices.

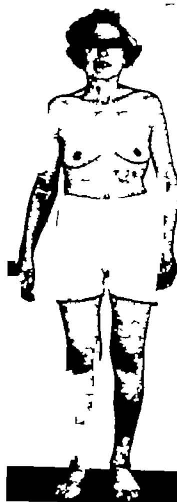
G Histograms of fibre diameters (bove) right brachial biceps of the patient, mean diameter 53 µm (SD 15 µm, 204 fibres) (below): brachial biceps of three normal *females 43—62 years of ge, mean diameter 49 µm* (SD 12 µm, 388 fibres) The broken lines indicate the verage diameter of normal muscles plus nd minus 2 times the standard deviation.





H





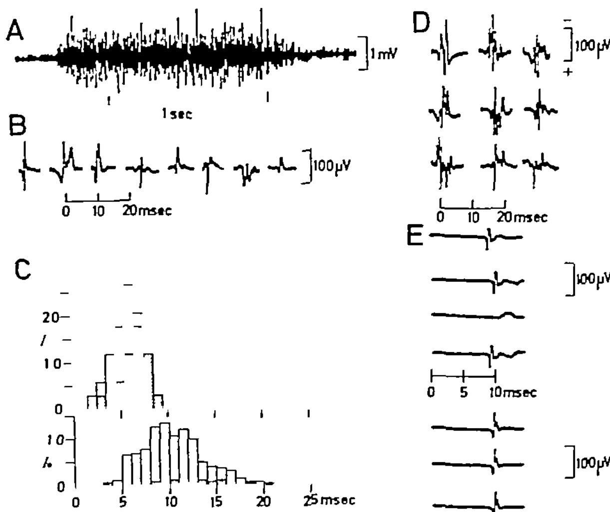


Fig. 14. Electromyographic findings in the left brachial biceps (A—E) and histopathological findings in the right brachial biceps muscle (F—G).

Patient 694 with juvenile polymyositis (case report 3 page 38).

A. Interference pattern of diminished amplitude during full effort.

B. Samples of motor unit potentials of simple shape.

C. Distribution of the duration of motor unit potentials (above) in the patient, (below) in 13 normal subjects of the same age. The shaded columns represent polyphasic potentials (53 % of all potentials in the patient and 6 in the normal muscles). The mean duration of all motor unit potentials in the patient was 5.8 msec (SD 1.6 msec, 34 potentials). The mean duration in the normal muscles was 10.3 msec (SD 3.2 msec, 351 potentials). The mean amplitude of the randomly recorded motor unit potentials was 165 µV (SD 140 µV) in the patient and 150 µV (SD 100 µV) in normal muscles.

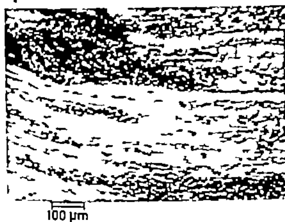
D. Samples of polyphasic potentials.

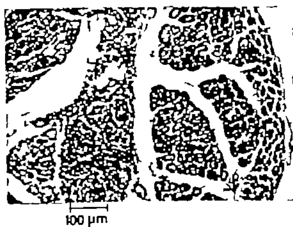
E. Spontaneous discharges (fibrillation potentials) were found at sites in the muscle.

F. (left) Longitudinal section showing inflammatory changes with loss of cross-striation. (right) cross-section with perivascularly localized inflammatory cells; the most atrophic fibres were localized to the periphery of the fasciculi. Haematoxylin-eosin stain, 5 µm slices.

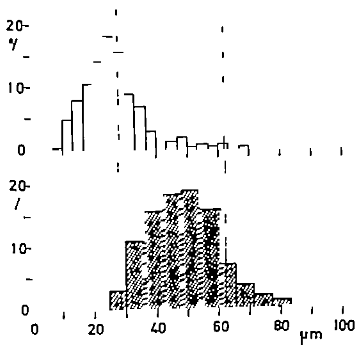
G. Histogram of fibre diameters (above): right brachial biceps of the patient, mean diameter 27 µm (SD 10 µm, 195 fibres), (below): brachial biceps of three normal females 43—62 years of age, mean diameter 49 µm (SD 12 µm, 388 fibres). The broken lines indicate the average diameter of normal muscles plus and minus 2 times the standard deviation in normal muscle.

F





G



H



3) **Juvenile polymyositis.** (Fig 14) Patient 694 16-year-old female without family history of neuromuscular disease. At 14 years of age she had a 7-day-period of fever headache and muscular pain, followed by weakness f the thighs and arms a d difficulty in flexing her neck. There were paraesthesia i the area supplied by the femoral cuta eous nerves

Neurological examination. 3 months after the onset of the disease there was slight erythema around the eyes, mild weakness and wasti g of the muscles of the shoulder and hip girdle. Th tendon jerks were present, the knee jerks were relatively weaker than the ankl jerks.

Laboratory findings The sedimentation rat was no mal there was intermittent leucocytosis (6 000—?7 000) serum alpha 2 globulin was increased, the antinuclear factor was slightly positive and lectat dehydrogenase was slightly increased (390 Wroblewski-units (normal 100—300)) Rheuma-serology was negative and LE-cells were bsent.

Electromyography 3 months after the onset of the disease there was 30—40 % decrease in mean duration of moto unit potential in the left brachial biceps (force 4) and in the left deltoid muscle (force 4) In both muscles there was marked polyphasia (?0—30 %) and a interference pattern of diminished amplitude during full effort.

Bi psies. A biopsy from the right lateral vastus nd the right brachial biceps howed perivascular inflammation The verage diameter was 35 % decreased in the brachial biceps nd the relative scatter of diameters was increased in both muscles. The trophic fibres were localized in the periphery f the fasciculi i both muscles (Fig. 11 C and 14)

The patient responded well to steroid treatment After ttack of mononucleosis 8 months l ter she relapsed and again sh responded well to steroid treat ment 1 year later after vaccination for influenza she relapsed gain and responded well to large doses of steroids. Af er that sh has relapsed again without a y known precipitating factor with more prono nced weak ness and wasting in the proximal muscles than before. 2 l ter electromyographic studies performed 26 nd 33 months after the onset f the disease showed th same degree of myopathic changes and ddition spontaneous activity A biopsy taken 3 years after the onset of the disease showed severe inflammatory changes and fibrosis of the rterial wall (no necrosis of the media) w th narrowed lumen. There was wide scatter of fibre diameters.

4) **Systemic lupus erythematosus.** Patient 364 a 36-yea -old housewif with ut f m ly history of neuromuscular disease For 6 years she had ttacks of vasoconstriction of the fi gers d slight signs f rthritis in the pper extremities. These ttacks lasted for 3—4 days nd were associated with rectal temperature of 39—40°C They came abo t twice year later more ften and were accompanied by bilateral parotitis and dysaestesia the right chin. For one year there had been slowly progressive wasti g and weakness mostly in the arms. There was neither muscular pain nor cutaneous volvement.

Neurological examination There was decreased sensitivity t touch nd pi prick the area of the second and third branch of the right trigeminal nerve, probably co sequent to the parotitis Proximal and distal muscles f the upper limbs were wasted and weak, there was sl ght wasting lso in the lower l mbs but the force seemed normal Tendon jerk er normal All joint in the upper limbs and the metatarso-phalangeal joi ts showed painful swelling and there were contractures at the elbow wrist and fingers.

Laboratory findings. The sediment tion rate was increased (102—117 mm/hour), the haemoglobi was low (7 9 g), there was leucopenia (2200—3800) nd eosinophilia (6—13 %) LE-cells were positive several times. Rheuma-serology was positive. The total protei of the serum was slightly (13 %) and gamma globulin markedly increased (by 173 %)

Electromyography In the left brachial biceps muscle (force 4-) the mean duration and amplitude of the motor unit potentials were normal The incidence of polyphasic potentials was slightly increased (15 %) and there were fibrillation potential t four sites. The amplitude and pattern during f ll effort were normal.

Biopsies The average muscle fibre diameter was 24 % decreased in the brachial biceps and 23 % increased in the l teral vastus. The spread of diameters in per cent was normal, but it was increased in μm in the lateral vastus (16 μm normal < 14 μm) The cross-striation was lost in small reas in both muscles There were many inflammatory changes mainly perivascular The brachial biceps muscle had few fibres with internal uclei

She improved lowly on steroid treatment 6 months later the sedimentation rate nd haemoglobin were nor mal and the signs nd symptoms related to the joint were improved. 2 1/2 years later she again had an ttack of high fever arthritis nd parotitis. These sympt ms disappeared when the dose of steroid was temporarily increased. 9 months later she relapsed with fever arthritis, dermatitis a d stomatitis. The sedimentation rate was 19 mm/hour There was no anaemia, but there were leucopenia (1800) and positive l tex fixation test the Waaler Rose test was negative X-rays of the hands showed no b rmality

Electromyography i the left brachial biceps muscl (force 5) 4 years and 4 months after the first examination howed a 30 % decrease i mean d ration of the motor un t potential and more prono nced spontaneous ctivity th n t the first study with pseudomyoto ic bursts. There was a sl ghtly increased (14 %) incidence f polyphasic potentials.

5) **Periarteritis nodosa** (?) P tient 449 a 30-yea -old unskilled worker without fam ly history of neuromuscular disease had an acut illness with fever cough nd erythema over the legs. 12 days l ter he complained of tenderness i the extensor muscles f the forearms and of the right leg There was lso shifting bdominal pain. 1 month later he complained of paraesthesia i the right hand, l ter confined to digits I, II d III. Two months fter the onset of the disease he had gra d mal seizure and 10 days later repeated periods of confusion with hallucinations.

N urological examination There was mild weakness and marked tenderness particularly of proximal muscles f the arms and legs. The tend jerks were normal in the arms d absent i the legs. There was dysesthesia in the right digits I II and III

Laboratory findings. The sediment tion rat was increased (122 mm/hou), haemogl bin was diminished (9.3 g), there was leucocytosis (1 500—?6 100) Latex fixatio test was positive, total serum protein was normal, but albumin was decreased by 45 % nd alph 1 alpha-2 nd gamma-globulins were ncreased (by 70, 98 and 87 %) Serum glutamic oxalacetic transami ase was increased (2.4 units, normal < 1.8 unit) creatine phosphokinase nd lactate dehydrogenase were normal. LE

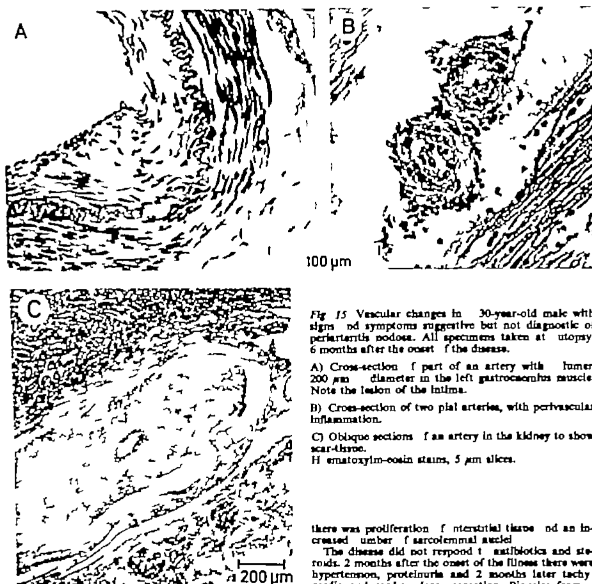


Fig 15 Vascular changes in 30-year-old male with signs nd symptoms suggestive but not diagnostic of periarteritis nodosa. All specimens taken at utopsy 6 months after the onset f the disease.

A) Cross-section f part of an artery with lumen 200 µm diameter in the left gastrocnemius muscle. Note the lesion of the intima.

B) Cross-section of two pial arteries, with perivascular inflammation.

C) Oblique sections f an artery in the kidney to show scar-tissue.
H ematoxylin-eosin stains, 5 µm slices.

cells were absent. The faeces contained blood. The electroencephalogram showed slow-wave focus with less than 1/sec with an mplitude of 200 µV over the right frontal region, later over the right occipital region. There were paro ysmal discharges over the right hemisphere. Air encephalography showed evidence of central trophy

Electromyography of the left brachial biceps muscle (force 4) showed spontaneous activity at 9 sites and an increased incidence of polyphasic potentials (18 %). The mean duration of motor unit potentials, their amplitude and the pattern during full effort were normal

Biopsies were taken from the right and left lateral astus muscles 1 1/2 months after the onset both showed inflammatory changes, diffusely in the right and focal the left muscle. The mea diameters were normal, the pread of diameters was increased in the left muscle. The cross-striation was lost in small reas nd there was proliferation f nterstitial tissue nd an increased umber f sarcolemmal nuclei

The disease did not respond t antibiotics and steroids. 2 months after the onset of the illness there were hypertension, proteinuria and 2 months later tachycardia and cardia decompensation Biopsies from lymph node, the liver nd the subcutaneous tissue did not give further information Autopsy 6 months after the onset of the disease showed acute fibrinous pericarditis, cuto oedema in the liver nd lu gs, per forated duodenal lcer and changes i blood vessels (Fig 15) but not the necrotizi g gitis typical of periarteritis nodosa. I muscle f the right leg the mea diameter of fibres was markedly decreased by 60 % the scatter of diameters was normal The trophic fibres dominated the picture nd the large fibres seemed to be i patches. There were few centrally localized uclei and the number f sarcolemmal uclei was sl ghtly increased The cross-striation w lost i small areas, the connective tissue wa slightly increased nd there were practically no inflammatory cha ges.

6) *Systemic scleroderma* Patient 965 was a 25-year ld male without f m ly hist ry of neuromuscular disease For 1 year he had complained of attack of acrocyanosis, pain nd paresthesias in the fi gers. For th

last months these attacks were frequent, up to 10 per day lasted 5—30 min, and ffected also the toes and ear lobes, and there was pain in all joints. There were ulcerations of the ski (tuber ischiadicum, olecranon, malleoli). For the past year there had been weakness of the muscles of the shoulder girdle and later also of the hip girdle. I recent months he had difficulty in lifting his head from the pillow He had lost 14 kg in 4 months

N urological examination. There was diffuse wasting and weakness, most pronounced in the proximal muscles. The force of flexion of the neck was decreased the force of extension f the neck was normal. The tendon jerks were weak. The skin was dry and tough and typical sclerodermial changes were present in the face and distally in the limbs. There was slight contractu e in the joints of the hands, wrists and ankles.

Laboratory findings. The sedimentation rate was increased (49—15 mm/hour) The serum enzymes were increased. creatine phosphokinase was 10 times normal and serum glutamic pyruvic transaminase 25 times no mal The antinuclear factor was positive. Rheumaserology was negative and LE-cells were absent. Serum electrophoresis was normal and X ray of the teeth showed widening f the peridontal space (Stafne and Austin 1944).

Electromyography of the right vastus lateralis (force 4) the left deltoid (force 4) and the left extensor digi torum communis (force 4-) showed normal duration and amplitude f motor unit potentials. All muscles had an increased incidence of polyphasic potentials (25—35 %). Spontaneous activity was absent and the pattern during full effort was normal.

Biopsy from the right vastus lateralis muscl (taken before the electromyography) showed small inflammatory foci as the only abnormality

7) **Polymyalgia rheumatica.** Patient 891 was a 70-year-old woman without f mily history of neuromuscular disease. For 1 year she had complained of pain and weakness in both arms, more on the left She complained f ttacks of headach and she had slight fever

Neurological xamination There were weakness and wasting i both arms, more on the left There was neither joint nor cutaneous i volvement. The tendon jerks were normal

Laboratory findings The sedimentation rate was increased (113 mm/hour) total serum protein was nor mal but albumi was decreased by 29 % and alpha 1 alpha-2 and beta-globulins were increased (by 60, 106 and 64 %) The electroencephalogram was slightly abnormal with 2—3/sec discharges over the left frontotemporal region. Biopsy of the ramus frontalis of the right temporal artery showed arteritis.

Electromyography The mean duration of motor unit potentials was decreased by 40 % in the left femoral rectus and brachial biceps muscles (force 3) The amplitude of these potentials was decreased to half and the incidence of polyphasic potentials was increased (25 %) in the femoral rectus and normal in the brachial biceps muscle. The pattern and amplitude during full effort were normal.

Biopsy in the right quadriceps femoris muscle showed slight diffuse nd perivascular inflammation and a slight increase i endomysial fat.

She improved on chloroquine and has since been free of symptoms for 3 years.

REFERENCES

Adams, R., Denny-Brown, D & Pearson, C. Diseases of muscle. A study in pathology pp. 556, Hoeber New York, 1953

Afifi, A. K. & Bergman, R. A Steroid myopathy A study of the evolution of the muscl lesion in rabbits. Johns Hopk. med. J 124·66—86 1969

Afifi, A. K., Bergman, R. A. & Harvey J C. Steroid myopathy Clinical, histologic and cytologic obser vations. Johns Hopk. med. J 123 158—174 1968.

Alarcón-Segovia, D & Brown, A. L. Classification and etiologic aspects of necrotizing angitides: An analytic pproach to confused subject with critical review of the evidence for hypersensitivity in polyarteritis nodosa. M yo Clin. Proc. 39:205—222, 1964

Andrews, F M Polymyalgia rheumatica. A biopsy and follow-up study Ann. rheum Dis. 24 432—438 1965

Anonymous. Arteritis, Nineteenth rheum. rev Arthr and Rheum 13:538—548, 1970.

Arkin, A. A clinical od pathological study f periarteritis nodosa. Amer J Path. 6·401—426, 1930.

Arundell, F D Wilkinson, R. D & Haserick, J R. Dermatomyositis and malignant neoplasms in dults. Arch. Derm. 82:772—775 1960.

Baehr G Klemperer P & Schifrin, A. A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis) Trans. Ass. Amer Phycns. 50·139—152, 1935

Banker B. Q Dermat myositis of childhood Trans. Amer neurol Ass. 87 11—15 196..

Banker B. Q & Victor M Dermatomyositis (syst mic angiopathy) of childhood Medicine (Baltimore) 45:261—289 1966.

Barber H. S. Myalgic syndrom with constitutional effects. Polymyalgia Rheumatica. Ann. Rheum. Dis. 16 230—237 1957

Barwick, D D. & W lton, J N Polymyositis. Amer J Med. 35·646—660, 1963.

Bäumer A. Klinisch Definition der Kollagenkrankheiten. Z. Rheumaforsch. 27.85—87 1968

Bekény G Changes in the skeletal muscles in scleroderma, pp 630—632 In: Muscle diseases, ed. Walton, J N Canal, N & Scarlato, S., pp 740 Internat. Congr Ser no 199 Excerpta Medica, Amsterdam, 1970.

Björkman, S. E. Phenylbutazone in the treatment of temporal Arteritis. Lancet 935—937 1958.

Bladh, W H., Bauer F K., Libby R. L. & Rose A. S. Studies in neuromuscular diseases with radioactive potassium. Neurology (Minneap.) 3.604—609, 1953

Bogaert, L. van, Radermecker M.-A., Lowenthal A. & Ket laer C. J Les polymyosites chroniques (essais vec l corthisone) Acta neurol. belg. 55 869—922, 1955.

Boylan, R. C. & Sokoloff L. Vascular lesions in dermatomyositis. Arthr and Rheum 3.379—386, 1960

Boyle, A C. & Beatty D C. Polymyalgia rheumatica. Proc. roy Soc. Med. 54.681—684 1961

Brown, J W., Nelson, J R. & Hermann C. Sjögren's Syndrome with myopathic and myasthenic features. Bull Los Angeles neurol. Soc. 33.9—20 1968

Bruce, W Senil rheumatic gout. Brit. med. J 2:811—813 1888

Buchthal, F An introduction to electromyography Scandinavian University Books, Gyldendal pp 43 Copenhagen, 1957

Buchthal F Spontaneous and voluntary electrical activity in neuromuscular disorders. Proceed. 8th Internat Congr Neurol Vienna, 2.15—45 1965

Buchthal F Electrophysiological bnormalities in metabolic myopathies and neuropathies. (Proceed. 19th Co gr Scandina Neurolog.) Acta neurol. scand. 46:suppl 43 129—176, 1970.

Buchthal F & Pinelli, P Analy is of muscle ction potentials as diagnostic aid in neuromuscular disorders. Acta med. scand. 142suppl. 266 315—327 1952.

Buchthal, F & Pinelli, P Muscle action potentials in polymyositis. Neurology (Minneap.) 3 4 4—436, 1953

Buchthal F & Rosenfalck, P Electrophysiological aspects of myopathy with particular reference to progressiv muscular dystrophy pp. 193—262. In: Muscular Dystrophy in Man and Animals, ed. Bourne, G H & Golarz, M N pp 524 Karger Basel, 1963

Buchthal, F & Rosenfalck, P Spontaneous electrical activity of human muscle. Electroenceph. clin. Neurophysiol. 20 321—336, 1966.

Buchthal F Schmalbruch, H & Kamieniecka, Z. Contraction times and fiber types in neurogenic paresis. Neurology (Minneap.) 21:58—76. 1971

Buchthal, F & Olsen, Zander P Electromyography and muscl biopsy in infantile spinal muscular atrophy Brain 93 15—30, 1970.

Bunim, J J A broader spectrum of Sjögren yndrome and its pathogenetic implications. Heberden Oration. Ann. rheum Dis. 20·1—10, 1961

Camp, W A. & Engel, W K. Myopathies associated with other diseases. Clin. Orthop. 39·19—33, 1965.

Caruso, G & Buchthal, F Refractory period of muscle and electromyographic findings in relatives of patient with muscular dystrophy Brain 88 29—50, 1965

Christianson, H B., Brunsting, L A. & Perry H. O

Dermatomyositis. Unusual features, complications and treatment. Arch. Derm. 74.581—589 1956.

Coërs, C. Sur quelques types cliniques et histologiques de polymyosites. Rev belge Path. 25.369—383 1956.

Coërs, C. & Hildebrand, J Latent neuropathy in diabetes and alcoholism. Electromyographic nd histological study Neurology (Minneap.) 15 19—38 1965

Copeman, W S. C. Introductory note on th nomenclature and classification of the rheumatic diseases pp. 12—18 In: Textbook of the rheumatoid dis eases, ed. Copeman, W S. C. pp. 959 Livingstone, Edinburgh 1969

Cruickshank, B. Focal lesions in skeletal muscles nd peripheral nerves in rheumatoid arthritis and other conditions. J Path. Bact. 64.21—32, 1952.

Curzio, C. Dissertation anatomique et pratique sur une maladie de la peau, d'une espèce fort rare et fort singulière (traduite de l'Italien), pp 136, Vincent, Paris, 1755

Degos, R., Garnier G Daruis, F & Vhslan, L. Lupus érythémateux subaigu avec signes frustes de dermatomyosite (troubles électromyographiques) Bull Soc. franç. Derm. Syph. 56 114—116, 1949

Delbarre, F Guiraudon, C., Bontoux, D & Saporta, L. Généralités sur les lésions vasculaires des mala dies du collagène. Rev Rhum 35:372—381 1968

Denny-Brown, D The nature of polymyositis and related muscular diseases. Trans. Stud. Coll. Phycns. Philad. 28 14—29 1960.

Diessner G R., Howard, F M. jr., Winkelmann, R. K Lambert, E. H & Mulder D W Laboratory test in polymyositis. Arch. intern. Med. 117 757—763 1966.

Dinkler M. Zur Lehre von der Sklerodermie. Dtsch. Arch. klin. Med. 48.514—577 1891

Ditzel J Relationship of blood protein composition to intravascular erythrocyte aggregation (Sludged Blood). Acta med. scand. 164:suppl. 343 pp. 63 1959

Dixon, A. St. J Polymyalgia rheumatica and poly chondritis, pp. 6.6—631 In: Textbook of the rheumatoid diseases, ed. Copeman, W S. C. pp. 959 Liv gstone, Edinburgh, 1969

Dubois, E. L. (ed.) Lupus erythematosus, pp. 479 Blakiston Division, McGraw-Hill New York, 1966.

Eadie, M. J & Ferrier T M Chloroquine myopathy J Neurol Neurosurg Psychiat. 29·131—337 1966

Eaton, L. M The perspectiv of neurology in regard to polymyositis. Neurology (Minneap) 4 245—263 1954

Ellis, J T Necrosis and regeneration of skeletal muscles in cortisone-treated rabbits. Amer J Path. 32: 993—1007 1956

Engel W K. Focal myopathic changes produced by electromyographic and hypodermic needles. »Needle Myopathy» Arch. Neurol (Chic.) 16 509—511 1967

Engel, W K. Selective and nonselective usceptibility f muscl fiber types. Arch. Neurol (Chic.) 22.97—117 1970

Erbslöh, F & Baedeker W D Lupusmyopathie. Dtsch. med. Wschr 48 464—2470 1962.

Erbslöh, F & Ebenburg, J Die Periarteriitis nodosa und ihr neuromuskulärer Schwerpunkt. Klin. Wschr 41:558—572, 1963

Fallet G H., Vasey H Meyer E. & Spahr J Les polyarthrites chroniques evolutives à cellules L.E. Rev Rhum. 26:553—578 1959

Faludi, G Gotlieb, J & Meyers, J Factors nfluenc ing the development f steroid-induced myopathies. Ann. N Y Acad. Sci 138 61—72, 1966

Fox, J T Sjögren's syndrom and late-life myopathy Arch. Neurol (Chic.) 15.397—398 1966.

Frohnert, P P & Sheps, S. G Long-term f llow-up study of periarteritis nodosa. Amer J Med. 43:8—14 1967

Garcin, R., Godlewski, S Gruner J Lapresl J & Lambert, P Sur les formes multinévritiques et polynévritiques de la périarterit noueuse. Étude de 7 observations inédites. Ann Méd. 56:114—147 1955 a.

Garcin, R., Lapresle, J Gruner J & Scherrer J Les polymyosites. Rev neurol. 92:465—510, 1955 b.

Gardner D L. Pathology of the connective tissue diseases, pp. 456, Arnold, London, 1965

Gintrac, E. Not sur la sclérodermie Rev Méd. Chi (Paris) 2.263—267 1847

Gordon, I., Rennie, A. M & Branwood, A W Poly myalgia rheumatica, biopsy studies. An rheum. Dis. 23·447—455 1964

Graudal H & Hvid, N An electromyographic study on patients with arthritis. Acta rheum scand. 5.34—41 1959

Greenfield, J G Shy G M Alvord, E. C. & Berg, L. An atlas of muscl pathology i neuromuscular diseases, pp. 104 Livingstone, Edinburgh, 1957

Guy E., Lefebvre J Lerique, J & Scherrer J Les signes électromyographiques des dermatomyosites. Étude de 9 cas. Rev neurol. 83.278—279 1950.

Hagström, J W C., Roseman, D M. & Ellis, J T Debilitating muscular weakness and steroid therapy A case with detailed clinical and pathological studies. Arch. Neurol. (Chic.) 5·60—67 1961

Hamrin, B., Jonsson, N. & Landberg, T Arteritis in »polymyalgia rheumatica» Lancet I.397—401 1964

Hamrin, B., Jonsson, N. & Landberg, T Involvement of large vessels in polymyalgia arteritica. Lancet I 1193—1196, 1965.

Hargraves, M. M Richmond, H. & M rton, R. Pre sentation of two bone marrow elements: the »Tart» cell and the »L.E.» cell. Proc. M yo Clin. 23.25—28 1948.

Hart, F The diffuse collagen (connective tissue) disrders, pp 574—588 In. Textbook of the rheuma toid diseases, ed. Copeman, W S. C. pp. 959 Livingstone Edinburgh, 1969

Harvey A. M., Shulman, L. E., T multy P A Conley C. L. & Schoenrich, E. H Systemic lupus erythematosus: Review of the literature and clinical analysis of 138 cases. Medicine (Baltimore) 33.291—437 1954.

Hathaway P W Engel, W K. & Zellweger H Experimental myopathy after microarterial embolization Arch. Neurol (Chic.) 22.365—378 1970.

Hausmanowa Petrusewicz, I & Jedrzejowska, H Correlation between electromyographic findings and muscle biopsy in cases of neuromuscular disease. J neurol. Sci. 13:85—106, 1971

Hausmanowa Petrusewicz, I & Kozminska, A Electromyographic findings i scleroderma. Arch. Neurol. (Chic.) 4.59—65 1961

Healey L. A., Parker F & Wilske, K. R. Polymyalgia Rheumatica and Giant Cell Arteritis. Arthr and Rheum 14 138—141 1971

Hepp, P Ueber einen Fall von acuter parenchymatöser Myositis, welche Geschwülst bildete und Fluctuation vortäuschte. Berl klin. Wschr 4.389—391 1887

Hinterbuchner C. N & Hinterbuchner L. P Myopathic syndrome in muscular sarcoidosis. Brain 87· 355—366, 1964

H lst, J E. & Johansen, E. A special type f rheuma tic disease. Acta med. scand. 122:258—270, 1945

Horvath, B., Berg, L. Cummings, D J & Shy G M Muscular dystrophy Cation concentrations in residual muscle. J appl. Physiol. 8.22—30, 1955.

Hunder G G Dhney T F & Ward, L. E. Polymyalgia rheumatica. Mayo Clin. Proc. 44.849—875 1969

Kaeser H E. & Kocher R. Iatrogene Muskelsymptome und Myopathien Ther Umsch. 27.387—393 1970.

Kaiser H Polymyalgia rheumatica, eine wenig bekannte, entzundlich-rheumatische Alterskrankheit. Munch med. Wschr 32:1609—1614, 1969

Kaposi, M. K. Neue Beiträge zur Kenntnis des Lupus erythematosus. Arch. Derm. 4.36—78, 1872.

Klevits, J H Goslings, J Schult, H. R. E. & Hijmans, W Rheumatoid arthritis and the positive L.E.-cell phenomenon. Ann. rheum. Dis. 15.211—215 1956.

Kinney T D & Maher M M. Dermatomyositis. Am J Path. 16:561—594 1940

Klemperer P The concept of collagen diseases. Amer J Path. 26:505—519 1950.

Klemperer P Pollack, A. D & Baehr G Pathology f disseminated lupus erythematosus. Arch. Path. 32:569—631 1941

Kogstad, O A. Polymyalgia rheumatica and its relation to arteritis temporalis. Acta med. scand. 178. 591—598, 1965

Kortan, J Woerkom, T van, Notermans, S., Kok, J Slooff, J Gabreëls, F & Prick, J Differential diagnostic considerations in patient with proximal muscular weakness. Psychiat. neurol. Neurochir (Amst.) 73 461—469 1970.

Korting, G W & Holzman, H. Die Sklerodermie und ihr nahestehende Bindegewebsprobleme, pp. 155 Thieme, Stuttgart, 1967

Kunze, K. Hypoxia. possible cause in the development of muscle diseases, pp. 327—331 In. Muscle diseases, ed. Walton, J N Canal N and Scarlato G pp 740, Internat. Congr Ser no. 199 Excerpta Medica, Amsterdam, 1970.

Kussmaul, A. & Maier R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit M rbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einher geht. Dtsch. Arch. klin. Med. 1 484—518 1866.

Lambert, E. H., Beckett, S., Chen, C. J & Eaton, L. M. Unipolar electromyograms of patients with dermatomyositis. Fed. Proc. 9·73 1950.

Lambert, E. H Sayre, G P & Eaton, L. M Electrical activity of muscl in polymyositis. Trans. Amer neurol. Ass. 79.64—69 1954

Lewin, G. & Heller J Die Sklerodermie, pp. 236, A. Hirschwald, Berlin, 1895

Libman, E. & Sacks, B. A hitherto undescribed form of alvular and mural endocarditis. Arch. intern. Med. 33 701—737 1924

Lovelace, R. E. Mononeuritis multiplex in periarteritis nodosa. Neurology (Minneap.) 14 434—442, 1964

Lovsh n, L L. & Kernohan, J W Peripheral neuritis in periarteritis nodosa. A clinicopathologic study Arch. intern. Med. 82:321—338, 1948

Maxeiner S. R., M Donald, J R. & Kirklin, J Muscle biopsy in the diagnosis of periarteritis nodosa. An evaluation. Surg. Clin. N Amer 32.1225—1233 1952.

Medical research council: War Memorandum No 7 Aids to the investigation f peripheral nerve injuries, pp. 48. H M. Stationery Office, London, 1943

Medsger T A., Rodnan, G P., Moossy J & Vester J W Skeletal muscle involvement in progressive systemic sclerosis (Scleroderma). Arthr and Rheum 11.554—568, 1968.

Méry H. Anatomie pathologique et nature de l sclérodermie, pp. 99 G. Steinheil, Paris, 1889

Meulengracht, E. Periarthrosis humeroscapularis med langvarig feber vægttab og stærkt forhøjet sænkningsreaktion (English summary) Nord. Med. 27 1569—1570, 1945

Meulengracht, E. & Schwartz, M The course and prognosis of periarthrosis humeroscapularis with special regard to cases with general symptoms. Acta med. scand. 143.350—360 1952.

Miescher P A. & Paronetto F Systemic lupus erythematosus, chapter 56, pp. 675—712. In. Textbook of Immunopathology ed. Miescher P A. & Müller Eberhard, H J 2pp. 805 Grune & Stratton, New Y rk, 1969

Miescher P A., Rothfield, N & Miescher A Immunologic phenomena in patients with systemic lupus erythematosus, chapter 6, pp. 93—103 In: Lupus erythematosus, ed. Dubois, E. L., pp. 479 Blakiston Division, McGraw-Hill, New York, 1966.

Milde, E. J & Tönder O Demonstration f rheumatoid f ctor in tissue by mixed gglutination with tissue sections. Arthr and Rheum. 11.537—545 1968.

Mills, J A. Connective tissue disease associated with malignant neoplastic disease. J chron. Dis. 16 797—811 1963

Moritz, U Electromyographic studies in dult rheumatoid arthritis. Acta rheum. scand. suppl. 5 pp. 123 1963

Moskowitz, R. W The histopathologic classification of periarteritis nodosa, study of 56 cases, pp. 103 Thesis, Graduate school, University of Minnesota, Minneap. 1960.

Müller R. & Kugelberg, E. Myopathy in Cushing s syndrome. J Neurol. Neurosurg Psychiat 22:314—319 1959

Muller H & Waldmann, G Morphologische Befunde bei Dermatomyositis. Arch. klin. exp. Derm. 230.304—318, 1967

Norton, W L. Comparison of the microangiopathy of systemic l pus erythematosus, dermatomyositis, scleroderma, and diabetes mellitus. Lab I vest. 22.301—308, 1970.

Norton, W L., Hurd, E. R., Lewis, D C. & Ziff M Evidence of microvascular injury in scleroderm nd ystemic lupus erythematosus: Quantitative study of the microvascula bed. J Lab. clin. Med. 71·919—933 1968.

O'Duffy J D Scherbel A L., Reidbord, H E. & McCormack, L. J Necrotizing angiitis. I A clinical review f twenty-seven utopsied cases. Cleveland Clin. Quart 32:87—98, 1965

O Leary P A., Lambert, E. H & Sayre, G P Muscle studies in cutaneous disease. J invest. Derm. 24 301—310, 1955.

Osler W On the visceral complications of erythema exudativum multiforme. Amer J med. Sci 110·629—646, 1895

Osler W On the visceral manifestations f the erythema group of kin diseases. Trans. Ass. Amer Phycns. 18:599—624 1903

Pagel, W & Treip, C S. Viscero-cutaneous collagenosis. A study of the intermediate forms of derma

tomyositis, scleroderma, and disseminated lupus erythematosus. J clin. Path. 8.1—18, 1955

Paronetto F. Systemic nonsuppurative necrotizing angiitis, chapter 59 pp. 722—732. In. Textbook of Immunopathology ed. Miescher P A. & Müller Eberhard, H. J 2:pp 805 Grune & Stratton, New York, 1969

Parry C. H Hemiplegia, chiefly to all appearance of the secreting arteries of th left side, pp. 478—480 In. Collections from the unpublished medical writings, pp 590, Underwoods, London, 1825

Pearson, C. M. Polymyositis and related disorders, chapter 12, pp. 13—26, In. Disorders of voluntary muscle, ed. Walton, J N pp 628, Churchill, London, 1964

Pearson, C. M Polymyositis. Ann. Rev Med. 17 63—82, 1966.

Pearson, C. M & Rose, A S. The inflammatory disorders of muscle. Chapter 15 pp. 422—478 In. Neuromuscular disorders, ed. Adams, R. D., Eaton, L. M and Shy G M pp 813 Williams & Wilkins, Baltimore, 1960.

Pearson, C. M & Yamazaki, J N Vacuolar myopathy in systemic lupus erythematosus. Amer J clin. Path. 29·455—463 1958.

Pleasure, D E., Walsh, C. O & Engel, W K. Atrophy of skeletal muscl in patients with Cushing's syndrome. Arch. Neurol (Chic.) 22.118—1.5 1970.

Ramsay I. D Electromyography in thyrotoxicosis. Quart J Med. 34 255—267 1965

Rebeiz, J J Amyotrophy and cancer pp 383—391 In. Muscle diseases, ed. Walton, J N Canal, N & Scarlato, S pp 740, Internat. Congr Ser no 199 Excerpta Medica, Amsterdam 1970.

Reske-Nielsen, E., Coërs, C. & Harmsen, A. Qualitative and qua titati histological study of neuromuscular biopsies from healthy young men. J neurol. Sci. 10:369—384, 1970.

Richardson, A. T Clinical and electromyographic aspects of polymyositis. Proc. roy Soc. Med 49 111—114 1956.

Rodnan, G P & Benedek, T G An historical account f the study of progressive systemic sclerosis (diffuse scleroderma) Ann. intern. Med 57.305—319 1962.

Rodnan, G P & Medsger T A. Musculo-skeletal inv l ement in p ogressive systemic sclerosis (scleroderma). Bull. heum. Dis. 17 419—422, 1966.

Romberg, M H T phoneurosen, pp 75—81 In: Klinische Ergebnisse, ed. Henoch, E. & Romberg, M H pp. 202 Albert Förstner Berlin, 1846.

Rose, A. L. & Walt n, J N Polymyositis: A survey f 89 cases with particular eferenc to treatment and prognosis. Brain 89 747—768 1966.

Rowland, L. P Muscula dystrophies, polymyositis, and other myopathies J hron. Dis. 8.510—535 1958

Sacco G Buchthal, F & Rosenfalck, P Motor unit potentials t different ges. Arch. Neurol. (Chic.) 6. 366—373 1962.

Sackner M A. Scleroderma, pp. 174 Grune & Strat t n, New York, 1966.

Schwalbe, G & M yeda, R. Ueber die Kaliberver hältnisse der quergestreiften Muskelfasern des Menschen. Z. Biol. 27 482—516, 1890.

Shulman, L. E. Scleroderma (Systemic sclerosis), chapter 58 pp 717—721 In. Textbook f Immunopathology ed. Miescher P A & Müller Eberhard H J ..pp 805 Grune & Stratton, New York, 1969

Shy G M The late onset myopathy A clinicopathologic study of 131 patients. Wld Neurol. 3 149—158 1962.

Siegler J W Monto R. W Ensign, D C., Wilson, G M J Rebuck, J W & Lovett, J D The incidence of the L. E. cell phenomenon in patients with rheumatoid arthritis. Arthr and Rheum. 1 115—121 1958

Silberberg, D H. & Drachman, D A. Late-life myopathy occurring with Sjögren syndrome. Arch. Neurol. (Chic.) 6.428—438, 1962.

Sissons, H A. Investigations of muscle fibre size, pp. 89—95 In. Research committee of the muscular dystrophy group, pp 273 Pitman Medical London, 1963

Sissons, H A. Anatomy of the motor unit, pp 1—15 In Disorders of voluntary muscles, ed. Walton, N. J pp. 628, Churchill, London, 1964

Sjögren, H. Zur Kenntnis der Keratoco junctivitis sicca. Acta ophthal. (Kbh.) 11:suppl. 2, pp. 151 1933

Sjögren, H Some problems concerning keratoconjunctivitis sicca and the Sicca-Syndrome. Acta ophthal. (Kbh.) 29.33—47 1951

Small, J M & Gavrilescu, K. The serum protein changes in giant cell arteritis. J Neurol. Neurosurg. Psychiat. 26.257—261 1963

Sokoloff L. *Biopsy in rheumatic diseases.* Med. Clin. N Amer 45 1171—1180, 1961

Sokoloff, L. The pathophysiology f peripheral blood vessels in collagen diseases, pp 297—325 I The peripheral blood vessels, ed. Orbison, J L. & Smith, D E., pp 357 Williams & Wilkins, Baltimore, 1963

Sokoloff L., Wilens, S L., Bunim J J & McEwen, C.: Diagnostic value f histologic lesions f striated muscle in rheumatoid arthritis. Amer J med Sci. 219·174—182, 1950

Song, S. K., Shimada, N & Anderson, P J Orthogonal diameters in the analysis f muscle fibre size and f rm. Nature (Lond.) 200.1220—1221 1963

Stafne, E. C. & Austin, L. T A ch racteristic dental finding in acrosclerosis and diffuse scleroderma. Oral Surg. 30.25—29 1944

Steiner W R. Dermat myositis, with report f case which presented rare muscle anomaly but once described in man. J exp Med. 6.407—442, 1901—1905

Stertz, G Polymyositis. Berl klin. Wschr p 489 1916

Thompson, C. E. Polymyositis in children. Clin. Pediat. (Phila.) 7.24—28, 1968

Thompson, J M Bluestone, R., Bywaters, E. G L., Dorling, J & Johnson, M Skeletal muscle involvement in systemic sclerosis. Ann. rheum. Dis. 28. 281—287 1969

Tomlinson B E., Walton, J N & Rebeiz, J J The effects f ageing and of cachexia upon skeletal muscle. A histopathological study J neurol. Sci. 9·321—346, 1969

Tuffanelli, D L. & Winkelmann, R. K. Systemic scleroderma. A clinical study of 727 cases. Arch. Derm. 84.359—371 1961

Unverricht, H. Polymyositis acuta progressiva. Z. klin. Med. 12:533—549 1887

Vischer E., Kaeser H E., Kocher R. & Steiger U Polymyalgia rheumatica. Praxis 58.443—449 1969

Waaler E. & Milde, E J Is there relationship between giant cell arteritis with polymyalgia rheumatica and rheumatoid arthritis? Acta path. mic robiol. scand. 72.347 1968

Wagner E. Fall einer seltenen Muskelkrankheit. Arch. d. Heilk. 4.282—283 1863

Wallace, S. L., Lattes, R. & Ragan, C.: Diagnostic significance of the muscle biopsy. Amer. J. Med. 25,600—610, 1958
Walton, J. N. & Adams, R. D. Polymyositis, pp. 270. Livingstone, Edinburgh, 1958
Wells, R. E. jr. Rheology of blood in the microvasculature. New Engl. J. Med. 270,832—839. 1964.
Westphal, C. F. O. Zwei Fälle von Sclerodermie. Charité-Ann. 3,341—360, 1876.
Winkelmann, R. K.. Classification and pathogenesis of scleroderma. Mayo Clin. Proc. 46,83—91. 1971
Winkelmann, R. K., Mulder, D. W., Lambert, E. H., Howard, F. M. & Diessner, R. O. Course of dermatomyositis-polymyositis: comparison of untreated and cortisone-treated patients. Mayo Clin. Proc. 43 545—556, 1968
Woolf, A. L. Muscle biopsy. pp. 11—35. In. Modern trends in neurology ed. Williams, D. pp. 384 Butterworths, London, 1962.
Yates, D. A. H. The estimation of mean potential duration in endocrine myopathy. J. Neurol. Neurosurg. *Psychiat.* 26:458—461. 1963
Zeek, P. M.. Periarteritis nodosa. critical review. Amer. J. clin. Path. 22,777—790. 1952.
Zeek, P. M., Smith, C. C. & Weeter, J. C.: Studies on periarteritis nodosa. III. The differentiation between the vascular lesions of periarteritis nodosa and of hypersensitivity. Amer. J. Path. 24:889—901. 1948

SUBJECT INDEX

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Supplementum 541

Diabetic Angiopathy and Neuropathy

A Review with Special Reference to
Circulation in the Extremities
The effect of Hypophysectomy on Capillary Resistance and Capillary Permeability
Functional Abnormalities in Early Diabetes

By Niels Juel Christensen

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Diabetic
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From the Second Clinic of Internal Medicine,
Kommunehospitalet, Arhus, Denmark

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By

Niels Juel Christensen

To Merete
Anne and Sigrid

CONTENTS

PREFACE

The present study represents a part of the work I carried out during my appointment to the Second Clinic of Internal Medicine, Kommunehospitalet, Arhus, Denmark

To the head of that department, Professor Knud Lundbæk, I wish to express my profound gratitude for ideal working conditions in a most inspiring atmosphere and for much valuable help and criticism.

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Arhus 1971

Niels Juel Christensen

Chapter 1

INTRODUCTION

Patients with diabetes mellitus of long standing frequently have complaints localized to the extremities, particularly to the lower extremities. On physical examination a number of abnormalities are often found. The extremities in man are easily accessible for physiological investigations, and biopsy material of the tissues can easily be obtained. For these reasons a considerable number of studies have been performed on the extremities of diabetic patients. Many different aspects of the diabetic disease have been elucidated. In most cases, however the investigators have been concerned with abnormalities present in long-term diabetic patients. A significant, although smaller amount of work aims at clarifying various abnormalities present in patients with recently diagnosed and untreated diabetes. Few studies have so far been performed in diabetics hypophysectomized for diabetic retinopathy

The various investigations of diabetic angiopathy and neuropathy might be divided in four main groups:

1 Clinical studies.
2. Radiological studies.
3 Morphological studies.
4 Functional studies.

The purpose of the present review is to summarize and discuss a number of functional studies of diabetic angiopathy and neuropathy in the main limited to examinations of the extremities. Diabetic angiopathy and neuropathy in other organs (retina, kidney and heart) will only be discussed to a limited extent and only as far as common pathophysiological mechanisms might be involved (chapter 3 and 4)

The functional studies may be divided into the following three groups:

1 Circulation and nervous function in long term diabetics. The studies included in this group are rather heterogeneous as regards both the subjects and the methodology and include examinations of blood flow in the extremities, arterial rigidity blood pressure, sweating capacity and purely neurophysiological studies. Only a part of the neurophysiological studies will be discussed in the present review

2. Capillary resistance and capillary permeability in long term diabetics.

3 The influence of the metabolic status on vessel and nerve function.

In this introductory chapter the clinical studies, the radiological studies and the morphological studies will be summarized briefly

CLINICAL STUDIES

Diabetic patients who have had the disease for many years frequently complain of pain and paraesthesiaes localized to the lower extremities. Physical examination often discloses loss of tendon reflexes, an increased vibratory perception threshold, loss of other sensory qualities and more seldom the so-called diabetic gangrene.

Steiness (222) and *Gregersen* (88) as well as

others have studied somatic neuropathy in diabetics.

In the following the most important studies on the incidence of peripheral vascular disease in diabetics will be mentioned briefly. As the same criticism can be directed at many of the reports, the individual series will not be discussed extensively but the main points and the conclusions will be gathered in a general discussion.

The early literature on diabetic gangrene was briefly summarized by *Kramer* (118). He collected data from earlier publications and found a total incidence of 756 cases of gangrene among 12,037 patients with diabetes mellitus (6 per cent). *Kramer* (118) also examined 1 008 case-records of diabetic patients and found 58 with gangrene or approximately 6 per cent. *Kramer* (118) as well as a number of earlier investigators expressed the view that a number of clinical findings separated diabetic gangrene from common senile gangrene. Diabetic gangrene sometimes occurred in the fifth decade. Inflamation was often present. Pain was not always a prominent feature and was sometimes absent. Normal pulsation in the arteries of the feet was sometimes found.

Leutenegger (128) studied 1 000 diabetic patients. A large proportion of the patients were less than 50 years of age. He found 31 cases of gangrene but in only one person less than 50 years of age. He did not believe that the frequency of peripheral vascular disease was increased in diabetic patients as he did not find any cases with gangrene among his younger patients with diabetes mellitus. He thought that the apparent high incidence of vascular disease in diabetics was due to their longer span of life after the introduction of insulin, permitting the diabetics to reach an age where vascular diseases also were common in non-diabet[illegible] In this connection it must be remembered that younger patients with long-term d[illegible] not common in those days.

Later many inv[illegible] studied the incidence of vascular diseases in diabetics and the frequency of diabetics among patients with peripheral vascular disease. A particular group of studies concerns the possible association between the presence of glucose tolerance-test diabetes and the presence of clinical vascular diseases of the heart and the lower extremities.

Dry & Hines (61) found 230 cases of clinical arterial insufficiency of the lower extremities among 7 073 diabetic patients but only 219 cases with peripheral vascular disease among 197 894 non-diabetics. The incidence was thus 3.26 and 0.11 per cent, respectively. Forty-nine per cent of the non-diabetic patients with vascular disease had gangrene as against 62 per cent among the diabetic patients. According to these authors peripheral vascular disease occurred one decade earlier in diabetics than in non-diabetics. The frequency of diabetic retinopathy was higher among the diabetic patients with peripheral vascular disease than expected in a group of diabetic patients. The ratio between the number of men and women with vascular disease was 7 : 1 in the non-diabetic group of patients but 2 : 1 in the diabetic group of patients. Unfortunately it is not clear from their study whether all the 230 diabetic patients had definite signs or symptoms of peripheral vascular disease or whether some of the patients demonstrated only diabetic neuropathy.

Using autopsy records *Bell* (19, 20) studied the incidence of gangrene in 59 733 non-diabetics and 2,130 diabetics who were more than 20 years of age. There were no cases of non-diabetic gangrene in persons less than 40 years of age and in only a few patients less than 60. In the non-diabetics in the age group 60–80 years the incidence in males and females was equal but there was a preponderance of men in those more than 80 years of age. The proportion of men to women with gangrene in the entire control series was 3 : 2. In the diabetic group only three persons developed gangrene before the age of 40. Approximately 14 per cent who died between the ages of 40 to 60 and about 24 per cent be

tween the ages of 60 to 80 years of age demonstrated gangrene. Gangrene was approximately 53 times more frequent in diabetic men and 71 times more frequent in diabetic women. More than 50 per cent of all cases with gangrene also had diabetes. No definite relationship could be established between the known duration of diabetes and the development of gangrene. The sex ratio was approximately one in the diabetic group of patients. The material is biased because it included approximately twice as many men as women.

Mårtensson (166) studied 221 patients surviving at least 15 years of diabetes. Gangrene or severe arterial insufficiency of the lower extremities was found in 19 per cent.

Lundbæk (134 135) studied a large group of patients with long-term diabetes (duration 15 years or more living in the municipality of Aarhus in the period 1924 to 1950) Gangrene was found in 7 per cent. In patients more than 60 years of age vascular disease of the legs in the form of absent pulsation of the arteria dorsalis pedis, gangrene or rubeosis plantarum was present in 58 per cent of those with diabetic retinopathy but in only 19 per cent of those without retinopathy *Lundbæk* (134 135) presented a number of reasons for regarding the various long-term diabetic manifestations as different expressions of one generalized, specific long term diabetic vascular disease localized to small and large arteries, to veins and capillaries. The vascular disease of long-standing diabetes was thus considered to be different from other chronic vascular diseases and called diabetic angiopathy

Oakley Catterall & Martin (173) studied the incidence of lesions of the feet in 3 788 diabetic patients. One hundred-and-forty-six revealed symptoms and signs of peripheral vascular disease but none were below the age of 40 and there were only three between the ages of 40 and 49 The incidence was greatest above the age of 60 years. No association could be demonstrated to duration of the disease Male diabetics were more frequently affected, especially in the older age groups.

The same authors also reported on a follow up study of some 250 diabetics in whom the disease began before the age of 15 years and in whom it had been present for 10 years and in many cases for more than 20 years. They were unable to find a single lesion attributable to occlusive vascular disease. Their conclusion was that the increased incidence of pedal lesions in diabetics was due to neuropathy or the superimposition of neuropathy on the degree of arterial disease common to non-diabetics of the same age and sex. These authors have recently re-emphasized this point of view (174)

Bryfogle & Bradley (27) studied 394 diabetic patients representing all age groups. The peripheral vascular lesions reported were those evidenced by visible lesions or intermittent claudication. Lesions secondary to neuropathic changes or due to infection occurring in the presence of what was clinically considered to be adequate peripheral circulation were excluded from analysis. Frank clinical evidence of peripheral vascular insufficiency was seen in 15 7 per cent. The age of those with peripheral vascular disease exceeded by far that of any group with neuropathy and retinopathy and averaged 62 years.

Kramer (119) reported on the incidence of peripheral vascular complications in 3,600 diabetic patients observed by him since 1921 Patients with peripheral vascular disorders were divided into three groups according to whether they had impaired circulation, threatening gangrene or gangrene. While the incidence of gangrene was unchanged since 1921 and ranged between 6 to 7 per cent, the incidence of impaired circulation had increased from 9 per cent to 47 per cent. No association with the duration of diabetes could be demonstrated From the period 1942 to 1956 859 out of 1 600 patients were considered to have peripheral vascular complications, but there was no case of gangrene in subjects less than 40 years and only 24 cases of impaired circulation and threatening gangrene Unfortunately the age distribution of the material is

not given The ratio of peripheral vascular disorders in the female group as compared to the male group was close to one

There seems to be no randomized popula tion study of the incidence of peripheral vascular disease in diabetics compared to non diabetics.

The frequency of diabetics among patients with peripheral vascular disorders has been reported by various authors.

As mentioned earlier in the study by *Dry & Hines* (61) approximately 50 per cent of all paitents with peripheral vascular disease had diabetes. In *Bell*'s study (20) more than 50 per cent of all patients with gangrene had dia betes mellitus.

Hines & Barker (98) found an incidence of diabetes of 20.3 per cent among 280 patients with peripheral vascular disease The incidence of gangrene was found to be higher in the diabetics compared to the whole group (76 per cent as against 54 per cent) Most of the diabetics had the moist type of gangrene secondary to infection.

Semple (203) found only six cases of diabetes among 100 patients with intermittent claudication A study was also made of 52 successive cases of gangrene admitted to the hospital. Twenty five of the 52 were diabetics. The mean age was approximately the same in the diabetics and the non-diabetics. Sixty per cent of the diabetics were women but among the 27 non-diabetics only three or 11 per cent, were women. *Semple* (203) also found that six of the 25 diabetics had intermittent claudica tion in addition to gangrene, whereas 20 of the 27 non-diabetics presented this symptom. This difference was significant. Arteriography was performed in eight diabetics and 18 non-diabetics. These results will be briefly discussed later

Berry & Flotte (23) studied the frequency of diabetics among 275 patients undergoing lumbar sympathectomy during the years 1945 –1952 Diabetes was found in 33 9 per cent but among patients less than 45 years only 15 per cent had diabetes. Eighty-two per cent of the diabetics had ulceration but only 55 per cent of the non-diabetics.

Le Fevre et al (127) found 141 patients or 28 per cent with diabetes among 500 patients with peripheral vascular disease.

Schadt et al (197) reported a follow-up study of 422 patients with the diagnosis of femoral artery occlusion based on symptoms and clinical examination. The incidence of diabetes in the group was 15.2 per cent. At the time of initial examination the mean age was identical in the two groups. Skin lesions were seen in 56.3 per cent of the diabetics on first examina tion but in only 20 9 per cent of the non diabetic patients.

Selvaag (202) studied 541 patients admitted to hospital for peripheral vascular disease and found that 9 6 per cent of the patients had diabetes. Although he considered this value to be higher than the prevalence of diabetics in the total population, he thought that it might be explained by the fact that the symptoms in the diabetic patients were more severe forc ing them to seek medical advice. In diabetics 32 4 per cent and in non-diabetics 7 4 per cent had gangrene and ulceration. *Selvaag* (202) doubted that diabetes mellitus accelerated the development or influenced the location of atherosclerosis* and he thought that the greater tendency to ulceration in diabetics might be due to an additional lesion of the small vessels.

Gensler et al (75) reported a study of 305 patients with vascular disease in the lower ex tremities of which 40 6 per cent had diabetes. The mean age in the diabetic group was higher than in the non-diabetics. The incidence of skin lesions of varying degree was much higher in the diabetic patients (49.2 as against 19.3 per cent)

A number of investigators have studied the relationship between clinical vascular disease and glucose tolerance (109 110 113 114 115 178 ?33 and others) The patients included

* defin tion f ath rosclerosis see page 23

in these studies did not have clinically diagnosed diabetes mellitus These studies as well as others clearly demonstrate that a reduced glucose tolerance is found more frequently among patients with atherosclerotic heart disease and atherosclerosis of the lower extremities than among healthy subjects. It is sometimes believed that the very slight hyperglycaemia present in these patients contributes causally to the development of the vascular disease. Although such a causal relationship is quite possible there is no direct evidence on this and one prospective study (178) throws some doubt on this hypothesis. If the slight hyperglycemia seen in non-diabetics with atherosclerosis had a causal effect on the development of the vascular disease then the vascular system must be more vulnerable to slight hyperglycaemia than the nervous system Young patients with glucose-tolerance-test-diabetes do not demonstrate the abnormal nervous response to ischaemia present in all diabetics (39) In patients with diabetes mellitus abnormalities of the nerves are seen very early after the onset of diabetes.

GENERAI DISCUSSION

The aforementioned studies indicate that the frequency of clinical vascular disease in the lower extremities is higher in diabetics than in non-diabetics (Table 1) Furthermore the frequency of diabetics among patients with peripheral vascular disease is higher than the prevalence of diabetics in the total population (Table 2) In all studies the frequency of ulceration and gangrene in patients with vascular disease is higher among diabetics than non-diabetics (Table 3) The studies mentioned above must be interpreted with caution. Unbiased incidence studies are very difficult to perform on hospital and autopsy material and generally the significance of errors is totally unknown (21 143) Control series are sometimes lacking which makes interpretation of the data difficult, particularly in cases where no correlation is obtained with the duration of diabetes. The reported high incidence of gangrene in diabetics in some of the studies might to a great extent be due to infection as this was common in diabetics some years ago.

Table I.

The frequency of peripheral vascular insufficiency among diabetics and non-diabetics

Authors	Non-diabetics (per cent)	Diabetics (per cent)	Comments
Dry & Hines (61)	0 1	3	
Bell (20)	0.3	19	gangrene, autopsy
Mårtensson (166)		19	duration more than 15 years
Lundbæk (134)		7	gangrene, duration more than 15 years
Semple (203)		42	signs
		10	signs and symptoms
Oakley Catterall & Martin (173)		4	
Bryfogle & Bradley (27)		16	
Kramer (119)		47	impaired circulation
		6	gangrene

Table II. *The frequency of diabetics among patients with peripheral vascular disease*

Authors	Diabetics (per cent)
Dry & Hines (61)	51
Hines & Barker (98)	20
Semple (203)	6
	48
Berry & Flotte (23)	34
Bell (20)	68
LeFevre et al. (127)	28
Schadt et al. (197)	15
Selvaag (202)	10
Gensler et al. (75)	41

intermittent claudication
gangrene

Table III. *The frequency of ulceration and gangrene among diabetics and non-diabetics with peripheral vascular disease*

Authors	Diabetics (per cent)	Non-diabetics (per cent)
Dry & Hines (61)	62	49
Hines & Barker (98)	76	54
Berry & Flotte (23)	87	55
Schadt et al. (197)	56	21
Selvaag (202)	32	7
Gensler et al. (75)	49	19

The contribution of infection is not so important to-day and the results obtained in earlier studies might not be relevant as regards the incidence of gangrene in diabetics at the present time.

Despite these critical comments it seems reasonable to state that there is considerable evidence supporting the opinion that the incidence of gangrene in the lower extremities is higher in diabetics than in non-diabetics. However, one has to admit that the pathogenetic role of vascular factors is obscure.

Gangrene occurs mainly in older diabetics and only rarely in younger patients even if they have had diabetes for many years. Thus the occurrence of gangrene in diabetics does not follow the same pattern as retinopathy for instance. This might, however, just indicate that additional factors such as the effect of age on the vascular system are necessary for the diabetic lesion to show itself in a clinical disorder.

A number of studies particularly those concerned with the incidence of diabetes among patients with peripheral vascular disease indicate that the diabetic patients are not younger than the non-diabetics. If diabetes influenced the development of vascular disease in the lower extremities one would expect that the diabetics in such studies would have a lower mean age. These observations contrast with the results obtained in studies concerned with the frequency of vascular disease among diabetics and non-diabetics. This paradox might be explained in several ways but it does, however, obscure the overall picture.

It appears from the above mentioned studies that so-called diabetic gangrene is not associated with the known duration of diabetes. This finding is of very little significance because it is easy to demonstrate (page 19) that other vascular phenomena in diabetics can often be shown to be correlated with the duration of diabetes in younger patients but not in the older age groups (in which gangrene mainly occurs). These observations might at least partially be due to the fact that the duration of diabetes is not well known in the older age groups. This assumption is supported by the correlation of retinopathy and gangrene in older patients which actually was observed in a few of the studies mentioned above.

Some studies indicate that there are an equal number of men and women among diabetics with so-called peripheral vascular disease. This finding is in contrast to the sex incidence among non-diabetics with vascular disease. In order to conclude from such observations that diabetes promotes the development of peripheral vascular disease, the sex incidence in the diabetic population must be known. Furthermore the explanation of the altered sex ratio in the diabetics is not neces-

sarily to be found in vascular factors per se but may be influenced by infection and neuropathy factors which are unlikely to be sex dependent.

In conclusion it can be said that gangrene and ulceration of the lower extremities appear to be more frequent in diabetics than in non-diabetics, but the significance of vascular factors is not clear It might be possible to obtain more information about diabetic vascular factors by studying younger diabetic patients. Firstly the duration of diabetes is well known in such patients and secondly vascular diseases are of little significance in young non-diabetics. Young diabetics do not demonstrate clinical vascular disease in the lower extremities or at least rarely do so For this reason, information can only be obtained by physiological examinations, e. g. measurements of blood flow in the extremities.

RADIOLOGICAL STUDIES

Radiological studies can be divided into two groups. a) x-ray films taken with the purpose of demonstrating arterial calcification. b) arteriographic studies in diabetic patients with clinical vascular disease

Labbe & Lefantin (120) pointed out that arterial calcifications were a frequent finding in diabetics. *Ferrier* (67) has briefly summarized investigations of arterial calcification up to 1964

White (238) reported on the frequency of arterial calcification in the lower extremities in a very large group of patients who were nearly all less than 50 years of age at the time of examination, most of them being between 30–39 years. With a duration of 15 years of diabetes the incidence of calcified arteries was 14 per cent, whereas it was 94 per cent after a duration of 35 years. With increasing age the frequency of calcification also increased, but the influence of age and duration of diabetes for the presence of arterial calcifications were not clearly separated.

Ferrier (67) studied 500 patients. Two-hundred-and-fifty were diabetics and 250 were non-diabetics matched for age and sex. Most of the patients were more than 50 years of age. Arterial calcification was divided into medial calcification and intimal calcification as suggested by *Lindbom* (130) Twenty per cent of the diabetics and 8 per cent of the control subjects had medial calcification at the knee level. This difference was significant. Intimal calcification occurred more frequently in diabetics than in non-diabetics, 14 per cent and 10 per cent respectively but this difference was not significant. In the diabetics arterial calcification of the medial type was also found more frequently in the arteries of the feet. In the younger group of patients, 20–49 years of age, a significant correlation could be established between the presence of arterial calcification and the duration of diabetes, although only a few patients had had the disease for more than 15 years. In the older age group no association was obtained with the known duration of the disease However in these patients the presence of arterial calcification was correlated to the presence of retinopathy

Christensen (36) studied radiologically demonstrable arterial calcifications in the lower extremities in 71 diabetic men between the age of 19 and 50 years and in 25 non-diabetic men matched for age Thirty-one per cent of the diabetic patients compared to 4 per cent of the non-diabetics had calcification, a significant difference. As expected, this abnormality was associated with the duration of diabetes. In all cases the type of calcification was medial and one patient showed intimal calcification in addition.

Neubauer (168, 169) has made a semiquantitative radiological study of arterial calcification in the lower extremities in a large group of diabetics and non-diabetics above 50 years of age. Medial calcification was found much more frequently in the diabetics than in the non-diabetics. No difference was found in the degree of intimal calcification in the two groups.

Thus there is sufficient evidence to state that arterial calcification of the medial type occurs much more frequently in diabetics than in non-diabetics, particularly in patients with long-standing diabetes regardless of age.

The important question is. what is the significance of this abnormality? Medial calcification is also present in non-diabetics, particularly in older patients and there is evidence from studies in non-diabetics that medial changes are not associated with clinically important intimal changes and luminal occlusion (54 130 157 195 211) As far as these results are relevant in diabetes, the conclusion must be drawn that the presence of this abnormality in diabetics is without any prognostic and clinical importance This point of view has recently been emphasized by *Malins (144)*

Accordingly one would not expect any correlation between blood flow in the extremities and the presence of medial calcification. This assumption is, however incorrect (36) and the significance of medial calcification in diabetes will be discussed later Whatever the significance of the medial calcifications found in diabetics may be, their presence indicates a morphological alteration of the large vessels which is correlated to the duration of the disease

The second type of radiological study in diabetics is the arteriographic investigation.

It has been mentioned earlier that *Semple* (203) in his study examined 52 successive cases of gangrene admitted to hospital Twenty five were diabetics and 27 non-diabetics. Arteriography was performed in 10 extremities among the diabetics and 21 extremities among the non-diabetics. The femoral and popliteal arteries were normal in nine of the 10 diabetic limbs studied but the crural arteries were frequently obstructed. The femoral or popliteal arteries were obstructed in all the non-diabetics except in two.

Other arteriographic studies indicate that occlusion of the crural arteries alone or in combination with obstruction of the femoral artery i e. so-called multiple occlusions, appears more frequently in diabetics than in non-diabetics (75 202)

see also footnote on page 3

MORPHOLOGICAL STUDIES

Histological studies can be divided into two groups: investigations of a) the arteries and b) the smaller vessels.

Larger vessels. Quantitative studies of gross lesions of the arteries in the lower extremities have not been performed in diabetics, at least not on a random sample *Moses* (163) and *Robertson & Strong* (191) studying the iliac vessels and the abdominal aorta, respectively found however a greater incidence in diabetics.

Hevelke (97) studied the ash calcium and cholesterol content of the brachial artery and femoral artery in diabetics and non-diabetics. At all age groups higher concentrations were found in the diabetic patients.

A number of studies have been performed with the purpose of demonstrating any possible morphological difference between arterial disease in diabetics and non-diabetics.

Hines & Barker (98) examined histologically the arteries of 32 amputated legs from diabetics and non-diabetics. No difference was obtained. The same conclusion was reached by *Lisa Magiday & Hart* (131) and by *Sappington & Fischer* (196)

Randerath & Die el (186) performed a histochemical study on arterial tissue removed at autopsy from 21 diabetic subjects with a mean age of 62 years and from 24 non-diabetics. According to these authors the most important difference was found in the intimal plaques of the muscular arteries. The concentration of acid mucopolysaccharides was apparently much higher in the diabetics than in the controls.

Strandness Priest & Gibbons (223) studied the pattern of arterial occlusion in amputated

extremities from 17 diabetics and 19 non diabetics. They found that the arteries of the legs were more frequently occluded in the diabetic patients than in the non-diabetics (81 per cent as against 57 per cent) Furthermore they noted that the aorta-iliac arteries were more frequently involved in the non-diabetics (27 per cent against 68 per cent) Both differences were significant.

Ferrier (68) studied 20 limbs (amputated because of chronic ischaemia) from 10 diabetic and 10 non-diabetic patients. The incidence of obstruction was identical in the two groups as concerns the larger arteries including the popliteal, tibial, peroneal plantar dorsalis pedis and plantar arch arteries. Medial calcification was found at all levels and was more widespread in diabetic arteries. In the metatarsal arteries luminal reduction was found to be much more frequent in diabetics (60 per cent against 21 per cent) In the total series a significant association could be established between severe medial calcification of the arteries of the feet and the presence of arterial obstruction, i. e intimal fibrosis.

Conrad (51) studied the occlusion pattern in 10 legs from diabetics as well as 10 legs from non-diabetic patients amputated for severe vascular disease. Casts were made of the vascular lumena by injecting acrylic plastic into the vessels. A semiquantitative expression for the degree of vessel occlusion was obtained by adding the per cent of total vessel length occluded completely to half the percent partially occluded. In the calf arteries the index tends to be higher in diabetics than in non-diabetics (62 per cent as against 52 per cent) but in the pedal arteries the index was less in the diabetic group of patients (6 against 12 per cent)

In summary it can be concluded that both the radiological studies and the histological studies indicate that arterial disease of the lower extremities is different in diabetics and non-diabetics. The main difference seems to be the presence of severe calcification of the media in the diabetics and a change in the pattern of arterial occlusion i. e. the distal arteries are apparently more severely affected in diabetes.

There are few studies of the development of arterial disease in animals with experimental diabetes and few experiments concerned with the effect of abnormal glucose metabolism on the metabolism of the arterial wall. Such studies are of great interest but will not be discussed here

Small vessel involvement. Modern investigation of morphological changes in smaller vessels in diabetics in the various tissues composing the extremities began in 1959 with the work by *Fagerberg* (64) and *Goldenberg et al* (77) Changes in the smaller intraneural vessels had earlier been reported by *Woltman & Wilder* (241) but they considered the morphological changes to be atherosclerotic.

Fagerberg (64) studied intraneural vessels in a large number of biopsies and in autopsy material obtained from the sural nerve of diabetics and non-diabetics and found increased vessel thickness and increased PAS stainability more frequently in diabetics, particularly in patients with neuropathy

Goldenberg & coworkers (77) studied sections from amputated extremities in 92 diabetics and compared the results with those found in various types of non-diabetics. They found enlargement of endothelial cells, cell proliferation and increased amounts of PAS-stainable material in the smaller arteries, arterioles and capillaries more frequently in diabetics than in non-diabetics and considered these changes important for the development of diabetic gangrene *Aagenæs & Moe* (1) found increased basal membrane thickness in skin capillaries from diabetics.

Several investigators have now studied the frequency of small vessel abnormalities in the various tissues of the extremities in diabetics and one review has appeared (217) On light microscopy an increased thickness of the walls of small vessels with greater PAS stainability has been found to occur more often in diabet

ies than in non-diabetics on electron-microscopy an increased thickness of the basal membrane has been reported (1 11 64 72, 77 151 161 180 181 190 224 232). The changes are apparently patchy and a few investigators have obtained negative results (68, 71)

The question which arises from these studies is: *What is the functional and clinical significance of the morphological alterations in the smaller vessels?* Two possibilities appear These changes could reduce blood flow inducing tissue ischaemia and thereby be responsible for the development of diabetic gangrene and play an important role in the development of diabetic neuropathy The other possibility is that these alterations are the morphological basis of the reduced capillary resistance and increased capillary permeability found in long-term diabetics (Chapter 3). *Fagerberg* (64) and *Goldenberg et al* (77) felt that microangiopathy was an important factor in the development of neuropathy and skin lesions in diabetics.

Moore & Frew (161) studied skin vessels in biopsies and amputated specimens in diabetics. The authors found lesions of the smaller vessels to be more frequent in patients with foot lesions than in those without. All the patients with foot lesions also demonstrated neuropathy or lack of peripheral pulsation. The patients with foot lesions were 10 years older than the patients without skin lesions, but the authors presented evidence that indicated that this difference was not important for the altered morphology of the small vessels.

Banson & Lacy (11) and *Funk* (72) found that lesions of small vessels were of the same degree in diabetics with and without gangrene.

Starr (217) reported briefly on a study of 20 amputated legs from diabetics In every case he found severe lesions of the greater arteries, particularly the more distal ones This could easily account for the gangrene He observed PAS-positive thickening of the walls of the capillaries more frequently in diabetic limb tissue The author pointed out that there was no striking narrowing of the smaller vessels in his patients and he considered it doubtful that the changes in the smaller vessels could be directly responsible for the ischaemic lesions of the feet.

Ferrier (68) who studied amputated legs from diabetic and non-diabetic subjects did not find any striking difference in smaller arteries, arterioles and capillaries between these two groups.

Conrad (51) who studied the occlusion pattern in amputated legs from diabetics and non-diabetics by injecting acrylic plastic into the vessels, rated small vessel occlusion in skin and muscle by grading the samples from 0–4 The average index of small vessel occlusion was 1 4 in diabetics and 1.8 in non-diabetics.

The extensive study by *Fagerberg* (64) indicated a good correlation between morphological changes in smaller vessels and nerves. Such a correlation between nerve damage and vascular alterations has, however not been very impressive in a number of other studies (35 58 83 190 226)

There seems to be no doubt that morphological alterations in smaller vessels in the extremities occur more frequently in diabetics than in non-diabetics. These changes might contribute to the development of diabetic neuropathy and gangrene but the morphological evidence for these proposals is not convincing. It is possible however that such evidence could be obtained by actual measurements of the blood flow in the extremities during various conditions. This would permit a simultaneous evaluation of the numerous vessels which supply oxygen to the tissue

There are no serious attempts to correlate morphological alterations in the smaller vessels with abnormal capillary resistance or capillary permeability

In summary the significance and nature of vascular factors responsible for the development of diabetic gangrene are not clear At least four explanations of pathogenesis have been proposed as well as various combinations of these

1) An increase in the frequency of atherosclerosis in no way different from that found in non-diabetics

2) An increase in the frequency of occlusion of the distal arteries in the extremities.

3) Small vessel involvement.

4) Diabetic neuropathy

In this review the word atherosclerosis signifies the very common and clinically important vascular disease of the intima found in otherwise healthy middle-aged and old subjects. The anatomy of this disease is characterized by fatty and fibrous plaques of the intima and there is often thrombotic occlusion of the arterial lumen. In the distal arteries of the lower extremities the intimal changes are frequently reported to be more fibrous than fatty. The word atherosclerosis is thus used differently here than it is by Marchand (148), who introduced the term, and Pickering (182), who made a review of terminology. Some authors do not include thrombotic lesion in the definition. On the other hand the present terminology is in accordance with the conception of many present day investigators.

The word arteriosclerosis (13?) is not used in the present context and need therefore not be defined.

As mentioned above many authors consider calcification of the media to be an independent lesion and different from atherosclerosis, an opinion in accordance with Monckeberg (165). Blumenthal, Lansing & Wheeler (24) found that medial calcification is more pronounced beneath the intimal plaques and consider the medial changes to be of primary importance for the development of intimal change. Mitchell & Schwartz (157) pointed out that arteries which show similar tendency to intimal plaque formation show widely different prevalences of medial calcification.

See also references 54, 130, 195 11 and the review by Y (243).

Recently the significance of the medial muscle cells for the development of atherosclerosis has been emphasized (76).

Chapter 2

CIRCULATION AND AUTONOMIC NERVOUS FUNCTION

The purpose of the present chapter is to summarize and discuss the various studies of blood flow and autonomic nervous function in the extremities in diabetes. No attempt will be made to describe circulation in healthy subjects. There are several recently published and excellent books on this topic

Classical venous occlusion plethysmography based on the principle of *Brodie & Russell* (26) is generally considered to be the most reliable method of measuring blood flow in the extremities. The procedure has been described in detail by *Barcroft & Swan* (15) *Greenwood* (85) and *Abramson* (5) Modifications of the classical technique can also be employed but a valid calibration procedure raises some technical problems. The local clearance method (112) employing ^{133}xenon (123) seems to be an important methodological advance This technique has recently been described in detail by *Lindbjerg* (129)

The studies to be reported in this chapter have been divided into two groups

1) Studies in which blood flow measurements either directly or indirectly are an essential part of the study

2) Other studies Arterial rigidity blood pressure [illegible] ting capacity

The subj[illegible] to be considered is somewhat complicated b[illegible]t the following main questions have to be answ[illegible]ed

1) Is blood flow red[illegible] the extremities in diabetes

It is not very likel[illegible] th[illegible] [illegible]ed [illegible] w reduced and there [illegible]re [illegible] question requires that blood flow be measured after vasodilatation. This principle is established from numerous studies of blood flow in non-diabetic subjects. The pathophysiological mechanism has been well explained by *Rau* (188) Although his considerations mainly refer to studies of large vessel disease the same principle must be valid in attempts to study small vessel involvement.

In the present context particular interest will be focused on investigations employing vasodilatory procedures which cause a response known to be little affected by a preexisting autonomic neuropathy The vascular responses to exercise and ischaemia are not dependent on an intact sympathetic innervation.

Furthermore questions as to whether this presumed impairment of circulation correlates with the duration of diabetes and the possible significance of involvement of smaller and larger vessels must be answered.

2) A number of the abnormal vascular responses reported in diabetic patients are normally elicited via autonomic nerve fibers. That is, a normal response depends on normal vessels and an intact autonomic innervation. Such abnormalities will be called neurovascular abnormalities. The presence of a neurovascular abnormality then raises the question as to what extent such abnormalities are due to vascular disease per se and to what extent they are caused by a disease of the autonomic nerves.

3) Is there a correlation in individual diabetic patients between impaired circulation [illegible]d the nerve lesion This question is relevant

for the long-debated problem whether or not vascular factors are significant for the development of diabetic neuropathy

BLOOD FLOW IN THE EXTREMITIES

Modern investigation of blood flow disturbances in the extremities of diabetics began with the studies of *Megibow et al* (152 153) *Handelsman Levitt & Conrad* (91) and *Mendlowitz, Grossman & Alpert* (154) These authors have since been cited numerous times in the literature because of their apparent demonstration of small vessel occlusion in diabetics.

Megibow et al (153) studied 47 diabetic patients less than 45 years of age None of them exhibited peripheral vascular disease as judged by clinical examination, x ray examination and oscillometry Unfortunately the duration of diabetes is not given. Blood flow was measured at both halluces by venous occlusion plethysmography before and after administration of nitroglycerine. An abnormal response was considered to be present when a large difference in blood flow was found at the two sides. The patients who responded abnormally received a ganglionic blocking agent and the authors considered a subsequent lack of rise in blood flow indicative of small vessel occlusion. Fifteen diabetics demonstrated small vessel occlusion according to these criteria. The authors interpretation of their data is perhaps questionable The initial lack of response to nitroglycerine correlates with an initial low resting blood flow This finding and the lack of vascular dilatation following nerve-block might indicate the presence of an asymmetrical, digital vascular disease The results can also be explained on the basis of a preexisting asymmetrical autonomic neuropathy It is well known that limb blood flow in patients without vascular disease increases after sympathectomy but returns to normal levels in two to three weeks. The actual size of the resting blood flow is dependent on local environmental temperature. Blood flow in such limbs will not respond to procedures which inhibit sympathetic tone, e. g. administration of ganglionic blocking agents or indirect heating (14 60 70)

Handelsman, Levitt & Conrad (91) studied the vascular response to intravenous administration of priscol as judged by skin temperature measurements in 16 diabetics and 11 non-diabetics. This work was criticized by *Barany* (12) and it would be unwise to draw any conclusions with relevance to diabetes from this study

Mendlowitz, Grossman & Alpert (154) studied 38 diabetic patients and 30 controls under the age of 50 years. None of the diabetic patients had retinal-vessel changes or calcification of the arteries in the lower extremities. All of them had had diabetes for less than 10 years. Circulation in the big toe was measured by calorimetry after one hour of indirect heating and administration of a ganglionic blocking agent. Nine of the 38 diabetic patients demonstrated a vascular response which was below the lower limit found in the control subjects. They did not believe that the low blood flow values could be due to residual neurogenic tone but thought that the changes represented an organic vascular lesion (155) It is obviously not possible in their study to distinguish vascular involvement from autonomic nervous involvement.

Martin (149) measured the skin temperature response to indirect heating and cooling on toe calf and thumb in 20 diabetics with symptoms and objective signs of neuropathy Nine patients initially demonstrated a high skin temperature in the feet but no vasoconstriction occurred in response to a 3-hour period of indirect cooling. Ten patients initially demonstrated a low skin temperature in the feet but no change was observed in response to indirect heating. On the contrary reflex vasodilatation invariably took place in the thumb Patients with an initially low skin temperature in the feet were also given priscol This drug

was chosen because previous investigations indicated that it produced vasodilatation independent of intact innervation. In all cases a prompt rise in temperature was noted. Thus *Martin* (149) has demonstrated the significance of autonomic neuropathy. *It is important to* realize that his results do not exclude the coexistence of a vascular disorder. Skin temperature reaches its maximal value at a time when the actual blood flow *just* exceeds normal resting values (66). *Martin* (149) believed that the finding of a high initial skin temperature in some diabetics and a low initial skin temperature in others indicated a selective destruction of vasodilator and vasoconstrictor nerves. It is, however accepted today that vasodilator nerves do not exist in the skin of the feet. Martin's interesting observation will be explained later.

Barany (12) studied 120 diabetic patients 15 to 30 years of age and a comparable group of non-diabetics. The vascular response to indirect heating was measured on the skin of *the lower extremities by calorimetry.* Heat dissipation was less in the diabetic group of patients and the degree of impairment correlated with the duration of diabetes. In 30 diabetics demonstrating an abnormal response to indirect heating in the initial experiment, he also examined heat-dissipation from the skin after nerve-blockade. No difference between the diabetic patients and the normals was *found.* Skin *temperature* was also *measured in* these patients and although the temperature rise was slower in the diabetics the final readings in the two groups were identical. In other experiments *Barany* (12) studied the sodium clearance from the skin and found a decreased response in the diabetic patients after nerve-blockade. *In these diabetics final* temperature readings were als[illegible] significantly lower than in the normals. On the ba[illegible] of the last two series of experiments *Ba*[illegible]*an*[illegible] [illegible]oncluded that the total circulation in th[illegible] [illegible] [illegible]s normal in the diabetics but the capil[illegible] [illegible] abnormal. There are, howev[illegible] [illegible]onsidering this conclusion d[illegible] [illegible]xact blood flow measurements cannot be obtained by the calorimetric method, although the minimal blood flow which could have conveyed the measured amount of heat can be calculated (84). It is, therefore questionable whether an *identical heat-dissipation indicates* identical blood flow values, at least at higher flow rates. Secondly it is obvious from the results presented that the total circulation, as judged from the skin temperature measurements, was not normal in the diabetic patients at the time when the clearance measurements were performed. The various abnormalities described by *Barany* (12) in the diabetic patients must be considered as *neurovascular abnormalities,* as *defined* above. The different calorimetrical responses to indirect heating and to nerve-blockade cannot be explained satisfactorily. But it is peculiar that final temperature readings after nerve-blockade were normal on one examination and highly significantly abnormal on another examination. *Barany* (12) made the interesting observation that blood pressure increased significantly *more in diabetics than in non-diabetics* after infusion of noradrenaline. The average fall in heat dissipation from the skin during infusion of adrenaline and noradrenaline was no greater in the diabetics, but return to the original level after the infusion was stopped was considerably prolonged. The mechanism which causes the increased sensitivity to catecholamines in diabetics can *probably be explained today.* It is most likely due to a destruction and lack of autonomic nerve fibers. It is well established that axonal uptake is an important mechanism of biological inactivation of the catecholamines. When the autonomic nerves degenerate the axonal uptake is impaired and the concentration of amines at the receptor sites increases (96, 237). Cocaine which blocks the axonal uptake also increases the biological activity of the catecholamines (231).

Sigroth (210) measured skin temperature on the fingers after indirect heating in 91 diabetics. Impairment was revealed in 53 patients. *Sigroth (210)* made the important ob-

servation that the temperature response to indirect heating could sometimes be normalized after a period of careful regulation of the blood sugar

Aagenæs (2) studied 120 diabetics and 40 non-diabetics of comparable age Only a few patients in both groups were more than 50 years of age. The vascular response to cooling and subsequently to indirect heating was measured on the toes and the dorsum of the foot using a thermoelectric thermometer *Aagenæs* (2) demonstrated that the rate of rise in temperature during indirect heating was slower in diabetics than in non-diabetics and that the degree of the abnormality was associated with the duration of diabetes at least up to 25 years. An interesting but statistically insignificant observation was the finding of a normalization of the temperature response in patients with diabetes for more than 25 years. *Aagenæs* (2) considered the abnormal rise in skin temperature after indirect heating to be due to autonomic neuropathy as well as to a vascular factor This conclusion was based on the finding of an association between the lack of rise in temperature during indirect heating and the presence of anhidrosis and between the temperature abnormalities and the presence of calcification of the arteries in the lower extremities as judged by x-ray examination. Microangiopathy was also proposed to play a role.

Weber & Wicht (235) studied the pulse volume in the toe in response to indirect and direct heating in 29 control subjects and in 28 diabetics without arterial disease based on pulse palpation and x-ray examination. As expected they found that the increase in pulse volume during the dilatation procedures was less in the diabetics than in the controls. It is surprising that many of the diabetics with an abnormal response had a very short duration of disease, less than 1 year Skin biopsies were also taken and the authors found that morphological alterations in the smaller vessles were more pronounced in those with an abnormal neurovascular response than in those with a normal response. Blood flow measurements were not performed

West et al (236) studied blood flow as measured by venous occlusion plethysmography in the calf and the feet in 77 healthy non-diabetics, 60 diabetics without clinical evidence of peripheral vascular disease and 25 non-diabetic patients showing gross clinical evidence of atherosclerosis. Unfortunately the age of the patients and the duration of the disease in the diabetics are not given. Blood flow was measured at rest and after infusion of adrenaline and in addition in the calf alone after a 2 minute period of ischaemia. In the foot they found that the resting blood flow and the decrease in flow after adrenaline were identical in the diabetics and non-diabetics. *Barany* (12) had earlier obtained the same results. They did not, however measure return of blood flow to resting level after the infusion of adrenaline had been stopped. As mentioned previously *Barany* (12) had demonstrated that the return of the flow to normal levels was considerably prolonged in the diabetic patients. *West et al* (236) demonstrated that the blood flow response to ischaemia (reactive hyperaemia) was identical in healthy subjects and in diabetic subjects. As expected the non-diabetic patients with peripheral atherosclerosis demonstrated a small increase in blood flow during the first minute of reactive hyperaemia. The authors made the interesting observation that the increase in calf blood flow during adrenaline infusion was significantly lower in diabetics than in the healthy subjects. They were not able to explain the phenomenon. They doubted that the abnormality could be due to autonomic neuropathy as no alterations in the blood flow response to adrenaline were found in either normals or in diabetics after sympathectomy and during epidural block.

Duff & S *un* (62) have, however demonstrated that the vascular dilatation normally seen after adrenaline infusion first disappears some time after sympathectomy i.e approximately 2 weeks after the operation. The abnormality is probably due to an increased sen-

sitivity of the alfa receptors which develops after sympathetic nerve degeneration. (See page 26)

Moorehouse Carter & Doupe (162) studied 12 healthy young subjects aged 18–25 years and 43 diabetic subjects aged 23–85 years with and without neurological signs. Using skin temperature measurements the authors evaluated the vascular response to procedures like indirect heating and cooling, local heat and cold as well as to adrenaline infusion. As expected they found that the reflex vascular response to heat and cold was often absent in diabetic patients with neurological signs. The local response to cold was studied by immersing the limb in a cold bath Sympathetic tone was released by indirect heating or by nerve blockade In normal persons these procedures were always followed by an increase in skin temperature exceeding that of the bath. In diabetic patients with absent vascular reflexes skin temperature remained low when the extremities were removed from the cold bath and no changes could be induced by indirect heating or nerve block. When these extremities were placed in a warm bath and then removed the temperature of the skin increased and remained warm that is when the limb was heated or chilled directly it remained so regardless of body temperature. *Moorehouse Carter & Doupe* (162) stated that the extremities were sensitive to cold. Furthermore, these investigators showed that the vessels of diabetics were hypersensitive to adrenaline, as had *Barany* (12) Like *Martin* (149) they demonstrated that while the vascular response to reflex stimulation often is absent in diabetics, application of a direct stimulus to the same vessels is followed by some vascular activity Thus the results clearly demonstrate the presence of autonomic neuropathy but the study does not exclude the existence of a vascular disease per se As mentioned before skin temperature will reach its maximal value at a time when the blood flow has only increased slightly It should be mentioned that skin temperature in diabetics might be influenced by anhidrosis which often is present in long-term diabetics (to be discussed later)

Munck et al (164) and *Karlefors* (107) measured maximal blood flow employing [133]xenon after ischaemic exercise in the anterior tibial muscle of 28 and 26 young diabetics, respectively Many of these patients had long-term diabetes and retinopathy No difference was found between diabetics and non-diabetics.

Säve-Söderbergh Angerwall & Fagerberg (224) studied the correlation between rise in toe temperature during indirect heating and the morphological picture of skin vessels which were obtained by biopsy from the dorsum of the foot. Thirty-eight young diabetics were examined. Both parameters were frequently found to be abnormal in the diabetics, but no significant correlation could be obtained in individual diabetic patients.

Alexander Teusen & Mitzkat (7) studied blood flow in the forearm and calf at rest and after a 5-minute period of ischaemia. In addition they measured what was called the integrated capillary pressure The apparatus used was the plethysmograph developed by *Schroeder* (199) They studied 74 non-diabetics and 90 diabetic patients. Resting blood flow and blood flow during reactive hyperaemia were slightly higher in the diabetics compared with the non-diabetics. On the other hand, the maximal rise in integrated capillary pressure as well as the rate of rise per unit of time were significantly lower in the diabetics. These abnormalities were not associated with the duration of diabetes. They believed that their results indicated a decrease in the nutritive blood flow in the diabetics and a shunting of blood via arterio-venous anastomoses. These authors did not realize that the relationship between flow and volume also depends on the rigidity of the vessels. A simpler explanation would be an increased rigidity of the vessel walls in diabetics. This last mentioned abnormality is in fact present in diabetic patients, as will be discussed later The proposal that

an abnormal distribution of blood flow occurs in diabetics between nutritive channels and arterio-venous anastomoses is by no means new. This possibility was considered many years ago by *Popoff* (183) and later by *Barany* (12). It is a fascinating hypothesis, but as regards the extremities in diabetics there is no convincing evidence.

The problem could be studied by employing microspheres of human serum albumin (133). The results of a study of the relationship between capillary filtration and total blood flow might not be valid in the present situation because capillary filtration may not be normal in diabetics (as discussed later).

Christensen (36) studied 75 diabetic men and 41 non-diabetic men. Their ages ranged from 19–50 years and the mean age was identical in the two groups. The duration of the disease ranged from less than one to 35 years. Blood flow in the anterior tibial muscle was measured by the ^{133}xenon method at rest and after ischaemic exercise. A supramaximal vasodilatation stimulus was employed (37). X-ray films were taken with the specific purpose of demonstrating arterial calcification. The mean maximal blood flow was significantly lower in diabetics compared to controls and decreased significantly with increasing duration of diabetes. The results obtained were further analyzed by dividing the patients into two groups according to whether they demonstrated arterial calcification (see page 19). In all cases medial calcification was found and one subject also demonstrated intimal calcification. In the group without calcifications the maximal blood flow was nearly identical to that found in the non-diabetic group of patients, irrespective of the duration of the disease. In the group of patients with calcification of the arteries there was a highly significant decrease in maximal blood flow with increasing duration of diabetes. Thus a low maximal blood flow was found in diabetic patients with a long duration of the disease and with arterial calcification of the media. The vibratory perception threshold in the big toe was also measured in the diabetic patients. The relationship between this parameter and the maximal blood flow will be briefly mentioned later.

Christensen (40) studied blood flow in the foot in 25 diabetic patients (age range 27–48 years, duration range 0–40 years) and in a comparable group of non-diabetics. Blood flow was determined by classical venous occlusion plethysmography. It was found that the so-called spontaneous variations in resting blood flow in the foot elicited by changes in the activity of the sympathetic nervous system were often absent or considerably reduced in the diabetics. This neuro-vascular abnormality was associated with the duration of diabetes. The vibratory perception threshold in the big toe of the diabetics was measured in order to evaluate the degree of neuropathy and the vascular response to 6-minute periods of ischaemia was measured in order to test the function of the vessels per se. As expected, the vibratory perception threshold was found to increase with increasing duration of diabetes. The postischaemic vascular dilatation (reactive hyperaemia) was significantly lower in the diabetics compared to the controls and decreased significantly with increasing duration of the disease. All patients but one with low post ischaemic peak flow exhibited severe medial calcification of the arteries. Multiple regression analysis was performed using the peak flow, the vibratory perception threshold and the duration of the disease as the three independent variables and the spontaneous variability in the resting blood flow as the dependent variable. The loss of variability was partially correlated with abnormal vibratory perception values and partially with a low peak flow. It was therefore proposed that the neurovascular abnormality was due to both a nervous factor (autonomic neuropathy) and to a decreased response of the vessels themselves. The former was found to be of greater importance.

Christensen (41) later reported on the relationship in individual diabetic patients be

tween the vibratory perception threshold in the big toe and the blood flow No relationship could be demonstrated between these two parameters in individual diabetic patients. Patients demonstrating a normal vascular response to ischaemia might have highly abnormal threshold values or normal threshold values and patients with an abnormal vascular response might have a normal threshold or abnormal values. It was concluded that it was unlikely that vascular factors could be of major importance for the development of this nervous abnormality

GENERAL DISCUSSION

The results of the studies discussed above are contradictory and confusing. It is possible to find supportive evidence in the literature for practically any hypothesis about vessel function in the lower extremities in diabetics. The suggestions range from one extreme to the other from the presence of small vessel occlusion in diabetics with a short duration of the disease to the presence of completely normal vessels even in long-term diabetic patients. There are several reasons for this state of inconsistency

Diabetic patients have been studied at different stages of their disease. Patients demonstrating arterial calcifications have for instance been omitted from some studies. Such results are not representative for diabetics generally There are methodological problems. Some of the methods employed for measuring blood flow do not give a reliable estimate of the actual size of the blood flow at least at higher flow rates, e g skin temperature measurements and calorimetry (66 84) This means that the finding of identical skin temperatures in diabetics and non-diabetics after procedures *which increase blood flow do not necessarily* allow the conclusion that the blood flow response is identical in the two groups (12 149 162) Another source of error lies in the interpretation of the results obtained after release of sympathetic tone (12, 153 155) A lack of vascular dilatation after appropriate nerve-blocking procedures or indirect heating does not imply a vascular lesion per se, but might just as well be due to a preexisting autonomic neuropathy This interpretation is in accordance with the fact that the blood flow in sympathectomized limbs returns to normal levels shortly after the operation. The blood flow in such limbs does not respond to indirect heating. Some studies (149 162) clearly indicate that this interpretation is relevant to a discussion of the circulation in the extremities of diabetics. It should be noted that diabetic patients with autonomic neuropathy also demonstrate loss of sensory nerve function. Circulation is somewhat different in sympathectomized limbs and denervated limbs. The main difference is that the sensitivity to cold is more pronounced in denervated extremities (60 209)

With these considerations in mind an attempt will be made to answer the questions put forward in the beginning of this chapter

1) Is blood flow reduced in the extremities of diabetics?

There seems to be some lack of agreement between the results obtained in studies of blood flow in the calf and calf-muscle tissue on one hand and the results obtained in skin and foot on the other *West et al* (236) *Munck et al* (164) and *Karlefors* (107) all reported normal blood flow values in the calf and calf muscle tissue in diabetics, whereas most studies of foot and skin blood flow have reported reduced values. This state of inconsistency is probably more apparent than real *West et al* (236) *Munck et al* (164) and *Karlefors* (107) employed methods of vessel dilatation which are little affected by a preexisting neuropathy This is not the case in many studies of skin and foot blood flow The results reported by *the authors mentioned above (107 164 236)* are however in contrast to those reported by *Christensen* (36) It is likely that the patients studied by *West et al* (236) had not had dia

betes for a period of time sufficient to allow the development of vascular changes and that the number of patients studied by *Munck et al* (164) and *Karlefors* (107) was too small. There might, however be a real difference in the rate of decline in blood flow in the calf and the foot in diabetics with increasing duration of the disease In the studies by *Christensen* (36, 40) maximal blood flow in the calf-muscle declined on the average 0 9 per cent for every year the patients had suffered from diabetes (as judged from regression analysis) In the foot the value was 2.1 per cent. There can be no reasonable doubt that maximal blood flow in calf-muscle tissue and the postischaemic blood flow in the foot are reduced in diabetics. The changes are correlated with the duration of diabetes, at least in younger patients (36, 40) A low maximal blood flow in muscle tissue is confined to patients demonstrating severe arterial calcification of the medial coat. In patients without calcification the maximal blood flow is normal, irrespective of the duration of the disease (36) The older concept of small vessel occlusion occurring early in diabetes and in patients without arterial lesions is not probable at least as far as muscle tissue is concerned. As to blood flow in the skin and foot the question cannot be answered as clearly It is obvious, however that convincing physiological evidence of small vessel occlusion even in these locations has never been obtained. Due to the experimental design, the abnormal responses obtained by some investigators and claimed to be indicative of the small vessel disease might just as well be interpreted as expressions of a preexisting autonomic neuropathy (12, 153 155) or as mentioned before, in other ways (7) In the study by *Christensen* (40) of reactive hyperaemia in the foot low blood flow responses were with the exception of one case only seen in patients with severe arterial calcification. A maximal stimulus to vessel dilation was probably not applied as the experiments were not designed to answer this question. If however a small vessel disease such as proposed by *Megibow et al* (153) *Mendlowitz* (155) *Barany* (12) and others really exists then its quantitative significance must be very limited compared to the large reductions in flow rates seen in patients with severe medial calcification The question might be answered definitely by studying diabetic patients without arterial calcification with the use of a combination of vessel dilatation procedures operating at a local level such as ischaemia, local heat and maybe others.

There are two additional questions.

Is there a relationship between lesions of small and large vessels in individual diabetic patients, i. e. do morphological alterations of the small vessels play a role in the reduction of blood flow found in patients with severe arterial calcification? It would not be unlikely if both groups of vessels were severely affected in the same patient. According to *Deckert* and *Poulsen* (53) the frequency of so-called atherosclerotic changes in the lower extremities in young diabetic patients is approximately identical in patients with slight and with severe small vessel disease of the retina and kidney Unfortunately in this investigation the signs of arterial disease were not measured quantitatively It might be of interest to study the correlation between retinopathy and maximal blood flow in calf-muscle tissue in diabetics.

The second question concerns the nature of the arterial disease. It must be stressed that calcification in diabetics is of the medial type It is remarkable that the presence of medial calcification in non-diabetics is generally accepted as an innocent finding without any functional or prognostic significance and that it occurs independently of intimal changes (54 130 157 195 211) Obviously diabetic patients differ in this respect, although there is no reason to believe that the increased peripheral resistance seen in diabetics is due to the medial changes per se Diabetic patients with very low blood flow also demonstrate occlu

In recent study by Barner Kaiser & Wahlman (16) blood flow in the diabetic leg was measured after injection of papaverine and correlated with the degree of the arterial lesion.

vascular system of diabetics is abnormally rigid or stiff. This is not unexpected remembering that arterial calcifications are a frequent finding even in young long-term diabetics. The rigidity of the arterial system increases in non-diabetics with increasing age.

Lax & Feinberg (65 125 126) studied the configuration of the arterial pulse wave in the finger in more than 1000 diabetics as well as in a large group of non-diabetics. They found that diminuation to disappearance of the dicrotic segment of the pulse wave is a frequent finding in diabetics. In their latest study they reported on findings in 907 diabetic children (age ranging between 10 to 19 years) and in 203 control subjects. Retinal examination proved to be normal in all cases. Seventy three per cent of the diabetics had an abnormal pulse configuration as compared with 7 per cent of the controls. No difference was obtained between male and female subjects. The abnormality was correlated to the duration of diabetes. It must be emphasized, however that 72 per cent of their patients with a duration of the disease of less than three years (412 patients) showed an abnormal pulse wave. *Lax & Feinberg* (126) also reported on a high incidence of abnormal pulse waves (30 per cent) in 40 children and young adults with a family history of diabetes (glucose tolerance tests were not performed) and in only 8 per cent of a control group *Camarini Davalos* (31) found a high prevalence of pulse wave abnormalities in prediabetics, 52 per cent against 26 per cent in the controls. *Lax & Feinberg*s and *Camarini-Davalos*s results obtained in prediabetics were not confirmed by *Otto & Mauren* (179) They studied the configuration of the arterial pulse wave in 195 young diabetics (age less than 30 years) and in 192 controls. No difference was found in the incidence of pulse wave abnormalities in diabetics and non-diabetics. Thus *Otto & Mauren* (179) found it unlikely that any differences exist between young prediabetics and [illegible]ntrol

Alexander Nissen & M[illegible] ([illegible]) studied the acral pulse wave in di[illegible]be[illegible] employing a photoelectric-plethysmograph. They found that diabetics at all ages demonstrated a diminished dicrotic pulse wave. According to these authors the difference was not very evident in the younger age groups.

Huston & Abboud (102) studied changes in blood pressure after inhalation of amyl nitrite in diabetics and controls. They calculated the ratio between the fall in pulse pressure and the related decrease in diastolic pressure before reflex tachycardia appears. This parameter (the arterial rigidity index) is close to one as long as the pressure volume relationship in the arterial system is a straight linear function but in the older age groups the line curves towards the pressure axis and the index becomes positive Fifty diabetic patients between 16 and 84 years of age were examined. Twenty-nine diabetics had a rigidity index that was greater than the upper limit of normal and 21 had normal values. Retinopathy and calcification of the aorta were more frequent in those with an abnormal index.

Woolam et al (242) measured the pulse wave velocity in 52 diabetic persons ranging in age from five to 75 years, as well as in 87 healthy non-diabetics. None of the subjects examined had clinical arterial disease or hypertension. The pulse wave velocity increased with age and was higher in the diabetics in all but one age group The abnormality was not found to be correlated with the duration of diabetes.

Munck et al (164) studied the maximal blood flow in the anterior tibial muscle in diabetics and controls (employing the [133]xenon technique) and found that the latency time i.e. the time from release of the arterial occlusion until maximal blood flow was reached, was decreased in long-term diabetics. The authors suggested that the abnormality was due to a neuropathy *Karlefors* (107) and *Christensen* (36) also found a decreased latency time. *Karlefors* (107) suggested that the abnormality was due to high blood pressure. A more likely explanation is an increased rigidity of the vascular system (36)

BLOOD PRESSURE

Orthostatic hypotension in the clinical sense is not a common finding in an unselected group of diabetics. An abnormal fall in systolic pressure on standing (with and without symptoms) is, however frequently seen in patients with severe neuropathy (2, 22, 176 194) According to *Aagenaes* (2) pulse response on standing is normal or exaggerated in diabetics with orthostatic hypotension indicating that both the afferent part of the reflex arc and the efferent arc to the heart are intact. In this way diabetics differ from patients with the Bradbury-Eggleston type of orthostatic hypotension. A normal increase in pulse on standing was also found by *Rundles* (194) whereas *Berner* (22) and *Odel Roth & Keating* (176) considered the increase to be insufficient.

Sharpey-Schafer & Taylor (208) examined the circulatory reflex response to the Valsalva manoeuvre in 337 diabetics. Seventeen showed complete absence of circulatory reflexes, i. e. no acceleration of heart rate during blowing and an absence of the overshoot in blood pressure and slowing in heart rate immediately after the procedure. Most of these patients were more than 50 years old and no correlation was obtained with the duration of the disease. These investigators considered the afferent reflex arc to be damaged in the diabetics. Their evidence for this is clearly insufficient and has frequently been criticized. It is generally overlooked that their patients did not show any change in heart rate during the procedure. This cannot be explained solely by a destruction of the peripheral efferent nerves but must imply damage to either the efferent cardiac nerves or to the afferent baroreceptor nerves. A central lesion could, however also explain the phenomenon.

Nathaniels & Ross (167) studied the pulse rate response to the Valsalva manoeuvre in 24 diabetics with the aid of electrocardiography and found reduced responses in diabetics, which were correlated with the duration of the disease.

Shapiro Moutsos & Krifcher (207) studied blood pressure changes in diabetics in response to the cold pressure test and after intravenous injection of angiotensin. They reported that diabetic patients were less reactive to the cold stimulus but more responsive to the infusion of angiotensin. The former abnormality in the diabetics is probably due to autonomic neuropathy because it is known that the pressure response to cold is mediated through the sympathetic nervous system. The increased sensitivity to angiotensin might perhaps also be explained by autonomic neuropathy i e a decreased compensatory effect of the baroreceptor nerves. The slowing of the pulse rate following the injection of angiotensin was significantly reduced in the diabetic patients.

Karlefors (107) studied blood pressure at rest and during exercise in a large group of diabetics and non-diabetics. Most of the subjects were less than 50 years of age. Rise in systolic pressure was more pronounced in the diabetics, particularly in those who had had diabetes for more than 15 years. It is interesting that an increased response to moderate-to-severe exercise was seen in a group of diabetics without retinopathy and in whom resting blood pressure was normal. *Karlefors* (107) considered several possible mechanisms to explain these changes, such as decreased elasticity of the larger vessels, autonomic neuropathy as well as the renal damage.

SWEATING CAPACITY

Reduced sweating capacity or anhidrosis is not an uncommon finding in long-term diabetics (2, 13 79 149 176 194) The abnormality is correlated to the duration of diabetes and evidence of severe neuropathy is often present in the same patient (2) This reduced to abolished sweating capacity in diabetics is most severe in the lower part of the body especially in the lower extremities. *Barany & Cooper* (13) studied the pathophysiological mechanism of anhidrosis. They found that direct heating of the skin produced sweating in

areas where there was complete absence of a sweat-response to body heating. Their study also indicated destruction of the post-ganglionic nerve supply. Patients with anhidrosis complain of discomfort in warm weather. Drenching night sweats of the upper part of the body, perhaps as a compensatory phenomenon, are not infrequent in such patients (80). Profuse sweating is sometimes seen in localized areas on the skin of the feet in patients with neuropathy, even when the environmental temperature is normal. The mechanism is unknown.

In summary, the physiology of the circulation in the extremities of diabetics has been reviewed in the present chapter. The available data are contradictory and confusing, but a number of erroneous interpretation and methodological errors have been pointed out and a number of earlier observations explained. From our discussion it has become evident that two major components are present in long-term diabetes.

The first component is an arterial disease demonstrable in various ways and in younger diabetics, at least, correlated to the duration of diabetes. X-ray examinations show a high [illegible] of arterial medial calcification, and [illegible] rigidity of the vascular system [illegible] demonstrated by fairly simple methods. [illegible] most important change is a reduction in [illegible] flow particularly in the feet. The ar[illegible] disease of juvenile diabetics differs to some extent from atherosclerosis in non-diabetics of a comparable age but shares certain similarities with that of very old people. The reason why diabetics develop such severe arterial damage at an early age remains unknown but provides an important subject for further research.

The second component is the nervous disease. It, too, is most pronounced in the lower extremities and is similarly correlated to the duration of diabetes. Diabetic neuropathy may be due to either the metabolic disturbance per se or/and to a vascular disease of intraneural vessels. The results obtained by physiological experiments are, however, inconsistent with the hypothesis that ischaemia plays a major role in the development of diabetic neuropathy and suggest that further research on pathogenesis should be directed towards the significance of metabolic factors.

Physiological knowledge of the autonomic nervous system has increased considerably within the last ten years and the pronounced disturbances in autonomic nervous function in diabetics are likely to attract attention in the years to come.

Although it is true that both the nervous disease and the vascular changes are most pronounced in diabetes of long-standing, it is perhaps more important to emphasize that the spread is quite large, some patients developing severe changes in the course of a few years, others demonstrating only minimal changes after many years of the disease.

The third component of the long-term diabetic disease, capillary fragility and increased capillary permeability, will be discussed in chapter 3.

Chapter 3

CAPILLARY RESISTANCE AND CAPILLARY PERMEABILITY

Hanum (94) was the first to observe that skin capillaries are fragile in diabetics with retinopathy. This abnormality in diabetics has since attracted a great deal of attention and Hanum's finding has been confirmed by several other studies.

Beaser, Rudy & Seligman (18) studied capillary resistance in 121 subjects, mainly older patients, 54 of whom had diabetes. Twenty-one of the control subjects had hypertension and 15 of the diabetics. Fragile capillaries were found more frequently in diabetics than in non-diabetics and again more frequently in the hypertensive diabetics than in the hypertensive non-diabetics. *Beaser, Rudy & Seligman* (18) employed a venous stasis pressure proportional to the blood pressure, either the diastolic pressure or a pressure half way between diastolic pressure and systolic pressure. Although it is possible that the vessels become adapted to an increased pressure, it is unlikely that the arterial pressure influences capillary pressure to the same extent as the venous pressure due to the large pressure drop in the arterioles. It is therefore likely that the stasis pressure employed in these studies is higher also relatively in comparison with the arterial blood pressure in the hypertensives and that the values obtained in normotensives and hypertensives are not comparable. The investigators (18) finding of an increased capillary fragility in diabetics cannot, however, be criticized on this basis.

Mallory (145) studied skin capillary resistance in 120 diabetics and in 40 control subjects employing the venous stasis test (80 mm Hg) as well as the negative suction cup method. Thirty diabetics demonstrated an abnormal response in both tests but none of the control subjects did. Sixty-three per cent of the diabetics with retinopathy had abnormal values as against 7 per cent without retinopathy. The height of the blood pressure was not mentioned.

Foxworthy cited by *Wagener* (69) studied capillary resistance in 85 non-diabetics and 113 diabetics using the positive stasis test. Subjects with hypertension were excluded from the examination. The average time for the appearance of the first petechiae in the control subjects was 4.9 min., in the diabetics without retinopathy 2.4 min. and in the diabetics with retinopathy 1.5 min. The average number of petechiae appearing in a circle after 10 min. stasis was 14, 41 and 101 respectively.

Rodrigue & Root (192) reported a study of skin capillary resistance in 100 unselected diabetic patients and a selected group of 56 patients with retinopathy. The Göthlin positive pressure test was employed (35 mm Hg for 15 min. and 50 mm Hg for 15 min.). Capillary fragility was found to be abnormal in 40 of the unselected patients all but three of whom had diabetic retinopathy and/or hypertension. In the remaining 56 patients (excluding four in whom the results were considered to be borderline) with normal capillary resistance, only two had diabetic retinopathy. In the selected group of patients capillary resistance was not found to be normal in any case. The influence of age on capillary resistance was

not clearly evaluated, but it is obvious that many of the patients with retinopathy and in creased capillary fragility were less than 40 years of age No difference between males and females was observed in their study

Cometta & Cuendet (50) and *Gandolfi* (74) also found increased capillary fragility in dia betics. *Gandolfi* (74) found the abnormality more frequently in those with retinopathy whereas *Cometta & Cuendet* (50) found no difference *Ortiz et al* (177) studied 50 diabetic patients with various degrees of retinopathy The Göthlin test was found to be normal in all cases.

Barnes (17) studied 220 diabetics and 50 controls. Approximately 50 per cent of the diabetics had hypertension. Fragile skin capil laries were found more frequently in diabetics than in controls. The incidence was higher in those with retinopathy than in those without. The highest incidence was found in those with hypertension and diabetic retinopathy

Post & Stickle (185) studied 59 diabetics in whom the disease had begun before the age of 15 years. Fifty four patients had retinopathy Capillary fragility increased with increasing retinal damage. These authors used a positive pressure halfway between systolic and diastolic blood pressure as the venous stasis pressure. The pressure employed was probably higher in those with severe retinopathy than in those with mild retinopathy because retinal damage also correlated with the degree of renal involvement. As mentioned earlier this procedure is questionable, except when one compares two groups of subjects with the same degree of hypertension

Lundbæk (134) demonstrated decreased capillary resistance in 3? per cent of an unselected series of patient fter a duration of diabetes of 15 to 25 year and found that it was more common in pat ent with retinopathy *Lundbæk* (134) considered the abnormal capillary resistance in the kin ndicat e of the generalized nature of th d vascul disease

Forstmann (184) stud apillary re sistance in 1000 diabetics and a large group of controls. A negative suction-cup technique was employed. Capillary resistance was signif icantly lower in the diabetics than in the con trols, particularly in the younger age groups. Decreased capillary resistance was correlated to the duration of the disease only in young diabetics. Capillary fragility increased with in creasing age and increasing blood pressure. The author found, however that in most of the younger patients the low capillary resist ance could not be explained by high blood pressure

Kornerup (116) summarized most of the published data regarding capillary resistance in diabetics up to 1955 He studied 376 diabet ics employing the Göthlin test. Diabetic retinopathy was present in 38 4 per cent of the patients and 29 5 had hypertensive retinal changes. The petechial index increased with the degree of hypertensive fundal changes as well as with the degree of diabetic retinopathy Analysis of data from cases where only one of the two retinal alterations was present showed that each of these parameters influenced the petechial index to approximately the same degree.

Wojciklewicz, Bicz & Szopinska-Ciba (240) studied skin capillary resistance in 40 young diabetics below the age of 40 years as well as in a group of older patients. In the younger age group capillary resistance decreased with increasing duration of the disease. This was not the case in the older age group.

Hart & Cohen (95) studied capillary resist ance in 88 non-diabetics and 211 diabetic patients using a combined positive and nega tive method. Low capillary resistance was a frequent finding in diabetic patients partic ularly in patients with retinal, arterial and neurological complications. An interesting observation was the finding that capillary fragil ity was correlated to the insulin dose the more insulin the patients received the lower the capillary resistance. The authors did not mention whether this correlation was influenced by the weight of the patients.

Hunter et al (101) reported a study of capillary resistance in three groups of diabetics as well as in a control group. None of the subjects examined had hypertension. They found a close correlation between capillary fragility and retinal haemorrhages in 50 diabetics below 50 years of age and with a duration of the disease of 15 years or more. In a second group of diabetics with deteriorating retinopathy capillary resistance was low in all cases. In a third group of diabetics with a duration of more than 15 years and with no visible retinopathy capillary resistance was high.

The aforementioned studies clearly demonstrate that skin capillaries are frequently fragile in diabetics. The abnormality is seen in patients with retinopathy and is most pronounced in those with severe retinopathy (17 18, 50 69 74 95 101 116 134 145 184 192, 240)

It is likely but yet unproven, that retinal haemorrhages and skin capillary fragility are caused by the same basic mechanism, one of the reasons being that these abnormalities are closely correlated in individual diabetic patients. Red dots can also be induced experimentally in the retina in long-term diabetics by increasing venous blood pressure (187) There are, of course morphological differences between skin capillaries and retinal capillaries but increased basal membrane thickness occurs at both sites It is also known that the tendency to haemorrhages in diabetics is not confined to retinal vessels (172)

The cause of the reduced capillary resistance in diabetics with retinopathy is unknown. It might be a functional expression of an altered capillary morphology (basal membrane? pericytes?) A decreased hyaluronic acid content of the skin might also be of significance. *Spiegelman & Herrera* (215) studied skin capillary fragility in diabetics before and after the injection of a hyaluronidase inhibitor The authors found that the anti-hyaluronidase preparation significantly reduced the number of petechiae which were elicited. The hyaluronic acid content of the skin is reduced in alloxan diabetic rats (198) The abnormality is not due to high blood pressure although this might be a contributary factor in some cases (17 18 69 101 116 134 184 192) The haemorrhagic features of hypertensive and diabetic retinopathy are different, but in hypertension a similar relationship exists between low skin capillary resistance and retinal haemorrhages (81)

In recent years several investigators have studied capillary permeability in various organs and tissues in diabetics.

1) Retina and iris: *Scott et al* (200) introduced fluorescein angiography in the study of diabetic retinopathy They showed that leakage of dye from retinal vessels is a frequent finding in diabetics with retinopathy *Jensen & Lundbæk* (105) and *Baggesen* (9) studied the iris. These investigators found that leakage of fluorescein from the vascular system of the iris occurs much more frequently in diabetics than in non-diabetics. According to *Baggesen* (9) this abnormality is particularly seen in patients with primary rubeosis iridis.

2) Whole body studies: *Ismail Khalifa & Madwar* (104) administered radio-iodinated serum albumin intravenously to 41 normals and 59 diabetics. The rate of disappearance from the plasma was measured by estimating the serum concentrations 1/2 hour and 3 1/2 hours after injection. The disappearance rate was significantly reduced in diabetics. They proposed that this was due to a reduction in capillary permeability in the diabetic patients. *Rossing* (193) reported in a subsequent letter that he, employing the same technique, had found no difference between 17 normal subjects and seven diabetics. No information on the duration of the disease in the diabetics was given in any of these contributions. *Rossing* (193) also emphasized the importance of using a non-denaturated preparation of radio-iodinated serum albumin

It seems probable that the results obtained after intravenous administration of the tracer

will chiefly depend on the condition of the fenestrated visceral capillaries.

3) Muscle tissue: *Spet* (214) studied 13 pregnant diabetic women between the ages of 18 and 32 years. In most cases the duration of the disease was less than 10 years. He found that the capillary filtration rate measured at rest in the forearm by plethysmography was significantly less in the diabetic women than in the non-diabetic pregnant women. The capillary filtration rate was not associated with the duration of pregnancy.

Alpert et al (8) in a recent abstract reported that the capillary filtration rate measured in the calf at rest was not altered in a small group of long-term diabetics with retinopathy, neuropathy and nephropathy. The resting capillary filtration rate is, however, difficult to measure, and these studies in diabetics should be repeated during conditions where the filtration rate is maximally stimulated.

Trap-Jensen et al (228) and *Trap-Jensen & Lassen* (229) studied capillary permeability in skeletal muscle in a group of long term diabetics employing the local clearance technique developed by *Lassen* (124). Capillary permeability to smaller ions was found to be significantly increased in diabetics who had had diabetes for many years. These authors interpreted their data in terms of increased permeability per unit area of capillary surface and thought it was less likely that the observed alterations were due to an enlargement of the total capillary diffusion area. This interpretation is supported by recent observations by the same authors (230) employing the indicator diffusion technique. They found that permeability was not altered to the same degree for substances with different molecular weights. This result indicates that the alteration in permeability cannot be explained by a simple enlargement of the total capillary diffusion area. The authors suggested that the width of *the inter-endothelial* [illegible] *in muscle capillaries* was increase[illegible] [illegible]erm diabetics.

Reske-Nielsen & [illegible] [illegible]90) reported that capillaries were [illegible] [illegible]n nor-mal in muscle tissue from long-term diabetics. Quantitative data has not been reported as yet.

Langer et al (121) studied the effect of exercise on haematocrit and plasma volume in diabetics. They found that the decrease in plasma volume and the increase in haematocrit were significantly greater in diabetics compared with control subjects. They believed that these changes were due to an altered capillary permeability but they also mentioned the possibility that the increased fall in plasma volume in the diabetics might be caused by the higher systolic pressure during exercise observed in these patients. In this connection it is pertinent to emphasize that the alterations in plasma volume during exercise are profoundly influenced by the blood pressure. Hypertensive non-diabetics show an increased response and no changes at all are seen if the rise in blood pressure is abolished by the administration of antihypertensive substances (92). Before it can be accepted that the increased fall in plasma volume during exercise seen in diabetics is due to altered capillary permeability the effect of the different response in diabetics as regards blood pressure has to be evaluated.

4) *Kidney*. A number of investigators have pointed out that the proteinuria often seen in long term diabetics suggests an increased permeability of the glomerulus. Proteinuria in long-term diabetics might not necessarily be the result of an altered glomerular function but could also be caused by an altered tubular cell function. *Mogensen* (158) studied urinary albumin excretion in short and long-term juvenile diabetics employing a sensitive radioimmunoassay. He found that excretion was normal in almost every patient with a duration of the disease ranging from 0 to 15 years. *Østerby* (244) found that the width of the glomerular basement membrane is already significantly increased in patients having had the disease for about 5 years which indicates that *morphological alterations of the basement* membrane precede albuminuria in diabetics. According to *Mogensen* (159) glomerular permeability determined by dextran clearance is

normal even in long-term diabetics with proteinuria, an interesting and unexpected finding.

The glomerular filtration rate in diabetics with recently diagnosed diabetes will be discussed in chapter 4

The aforementioned studies show that capillary permeability is abnormally high in long-term diabetics as regards the non-fenestrated capillaries in the retina (200) iris (9 105) as well as in muscular tissue (228 229 230) This finding is not unexpected, bearing in mind the well-established abnormality of capillary resistance As to the capillary permeability of the kidney Interpretation of the available data is still a matter of discussion, but it appears that glomerular permeability is not increased even in patients with proteinuria (159). It should be remembered that capillaries in the kidney are fenestrated and thus morphologically very different from capillaries in the retina and in muscular tissue. The mechanism responsible for the increased capillary permeability in diabetics is unknown, but the same possibilities might be considered as discussed in relation to capillary fragility

THE EFFECT OF HYPOPHYSECTOMY

Employing the positive venous stasis test *Christensen* (38) studied skin capillary resistance in a group of young diabetics hypophysectomized for the treatment of diabetic retinopathy as well as in a group of young non-operated, long-term diabetics. The patients were already participating in a controlled clinical trial of the effect of hypophysectomy on the development of diabetic angiopathy (139) Initially the two groups included 15 hypophysectomized patients and 15 non-operated, long-term diabetics. Allocation to the operated or the non-operated group had been at random and both groups of patients had been shown to be identical with respect to a large number of variables (139) Fourteen of the control subjects and 11 of the operated patients were available for study In 50 per cent of the control group the tourniquet test produced 10 or more petechiae in one or both of the two small skin areas examined. None of the hypophysectomized patients developed more than a few petechiae The difference was highly significant. Thus, this study demonstrated a notable increase in skin capillary resistance in long-term diabetics hypophysectomized for diabetic retinopathy

Since the low capillary resistance found in many long-term diabetics must be regarded as one expression of diabetic angiopathy the findings also demonstrate that hypophysectomy influences the development of this disorder at *sites outside the retina.*

Christensen (38) proposed that an increase in retinal capillary resistance by reducing the tendency to retinal haemorrhages could be one of the factors responsible for the beneficial effect of pituitary ablation on diabetic retinopathy (139 175).

At present, only one study of capillary permeability in hypophysectomized diabetics is available. *Balodimos et al* (10) performed retinal fluorescein angiography in diabetics with proliferative retinopathy treated with pituitary ablation These authors reported that abnormal leakage of dye from the retinal vessels decreases and eventually stops already a few weeks after hypophysectomy

Christensen & Terkildsen (45) studied the quantitative aspects of the change in capillary resistance following hypophysectomy in 16 hypophysectomized diabetics (137 139) 12 non-diabetic control subjects and in eight long-term diabetics with proliferative retinopathy The non-operated, long term diabetics were selected on the basis of the absence of arterial hypertension. Employing the negative suction cup method, 10 independent measurements of skin capillary resistance were performed on the medial side of the arm in each subject. Most of the non-diabetics had a mean capillary resistance between 160 and 190 mm Hg. One had a mean value above 200 mm Hg and one a value just below 150 mm Hg The mean capillary resistance for the whole group

was 176 mm Hg. As expected, all but one of the non-operated, long-term diabetic patients had low mean values, not exceeding 150 mm Hg. The mean for the group was 125 mm Hg and differed significantly from the value found in the normal control subjects. In most cases the hypophysectomized long-term diabetics had mean values higher than 200 mm Hg. None of them had a mean value lower than 150 mm Hg. The mean averaged 232 mm Hg. Capillary resistance was significantly higher in the hypophysectomized diabetics than it was in the normal controls and in the non-operated diabetic patients. Thus this study confirms and extends previous findings (38) The quantitative measurements of capillary resistance in hypophysectomized diabetics reveal that the values for skin capillary resistance were not only normalized but significantly increased

While non-operated, long-term diabetics with retinopathy have increased capillary fragility and capillary permeability hypophysectomy seems to reverse these abnormalities, although the mechanism of the increase and the decrease might not be the same It is possible that the increased capillary resistance in hypophysectomized patients is a functional phenomenon caused by a pronounced vasoconstriction (45) Recent studies have shown that plasma noradrenaline is considerably elevated in hypophysectomized long-term diabetics (44 46 47) A detailed discussion of the role of vasoconstriction and increased sympathetic tone in producing the beneficial effect of hypophysectomy on capillary resistance and diabetic retinopathy has been presented elsewhere (46 47)

The pituitary factor or factors ultimately responsible for the change in capillary resistance which occurs after hypophysectomy have not been identified Changes in body weight or blood pressure do not seem to have been of importance (38 45) Animal experiments (117) indicate that hypophysectomy can increase capillary resistance and that growth hormone tends to decrease it. Thus, abolition of growth hormone secretion in the hypophysectomized patients might be of importance in regard to the aforementioned changes (38) *

It has also been suggested that growth hormone plays a role in the development of diabetic angiopathy (140)

Merimee et al (156) have recently reported on a study of the incidence of retinopathy in 38 diabetics and in 31 sexual ateliotic dwarfs demonstrating a monotropic deficiency of human growth hormone and impairment of glucose tolerance. Forty-two per cent of the diabetics but none of the dwarfs demonstrated pathological changes in the retina. The degree of glucose intolerance was, however not comparable in the two groups. This is apparent not only from the fasting glucose values and the results of the glucose tolerance tests but also from the fact that most of the diabetics apparently needed treatment with insulin or sulfonylureas in contrast to the dwarfs. It would be interesting to know if the dwarfs demonstrated an increased capillary resistance.

In conclusion, fragility and increased permeability are characteristic capillary abnormalities in patients who have had diabetes for many years. Hypophysectomy is followed by a return to normal or even higher values for capillary resistance and by a decrease in capillary permeability It is probable that these changes explain the beneficial effect of hypophysectomy on diabetic retinopathy

Many more studies in diabetics of capillary

Circulatory changes in hypophysectomized diabetics fully substituted with cortisone and thyroid hormone are rather similar to the changes found in hypothyroidism, although the alterations are generally more pronounced in the hypothyroid patient (46, 47 49). Basal metabolic rate is reduced i both conditions (due to lack of growth hormone and thyroid hormones, respectively). Cardiac output is decreased and total vascular resistance increased (25 87). Capillary resistance is also above normal in myxoedema, perhaps due to vasoconstriction (227). Urinary excretion of noradrenaline is approximately doubled in such patients (239). These similarities as regards circulation, capillary resistance and noradrenaline raise the question as to whether hypothyroidism also would be of benefit on diabetic retinopathy (49).

permeability and fragility will be undertaken in the years to come in the attempt to answer the following questions. Firstly in what tissues are these abnormalities present, bearing in mind the very large variation in capillary morphology in different parts of the body Secondly what is the mechanism involved in the increase in capillary fragility and permeability—increased basal membrane thickness, pericyte abnormalities, loss of intercellular ground substance? Thirdly what is the mechanism by which hypophysectomy influences capillary resistance and permeability (vasoconstriction?)

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are, however of considerable theoretical interest.

For practical reasons the various abnormalities have been divided into two main groups 1) nervous abnormalities and 2) vascular abnormalities.

NERVOUS ABNORMALITIES

Steiness (219) measured the vibratory perception threshold in diabetics during artificially induced ischaemia. On the assumption that diabetic neuropathy is due to an inadequate blood supply to the nerves it was possible that artificial ischaemia would reveal incipient nervous lesions which were clinically latent. The author measured the vibratory perception threshold in the big toe and ischaemia was induced by inflating a pressure cuff placed above the knee. *Steiness* found (219) contrary to expectation, that diabetic patients perceived vibratory sensation during ischaemia for a much longer period than did control subjects. Many of the patients studied had been diabetic for less than 1 year at the time of the examination. Later *Steiness* (220) described the presence of the abnormality in patients with recently diagnosed diabetes and he made the observation that the phenomenon disappeared after a period of strict insulin treatment. *Steiness* (221) also showed that the abnormality could not be induced in non-diabetics by prolonged fasting, experimental hyperglycaemia or cortisone treatment.

Steiness's observations (219 220 221) have since been confirmed by other authors (34 39 86 204 225). This abnormality of ischaemic nerves has also been verified by measurements of the sensory nerve action potential (34 204).

Gregersen (86) showed that other sensory modalities such as touch and pain were retained significantly better during ischaemia in diabetics than they were in non-diabetics. The average fall in motor conduction velocity measured during ischaemia was significantly less in the diabetics than in the non-diabetics. Insulin treatment was accompanied by a change towards normal.

The ischaemic abnormality of nerves has recently been described as being present in isolated peripheral nerves of alloxan-diabetic rats (205).

Terkildsen & Christensen (225) studied the number of days of insulin treatment required to normalize vibratory perception threshold in the big toe during ischaemia in six young diabetics with recently diagnosed diabetes. The length of insulin therapy required averaged 18 days with a range of 12 to 31 days.

The cause of the ischaemic abnormality is unknown. *Steiness* (222) believed that the ability to perceive sensory transmission during prolonged periods of ischaemia in the diabetics was associated with an ability to maintain membrane polarization during a longer period of anoxia. *Gregersen* (86) mentioned the possibility that the phenomenon might involve the potassium ion (206) or the sorbitol pathway (73). The well known resistance against anoxia by the so-called non-myelinated fibers suggested that a functional or morphological defect of the myelin sheath might somehow explain the phenomenon. *Clausen & Christensen* (unpublished observation) considered the possibility that the abnormality was due to a decreased permeability of the cell membrane for sodium. The passive influx of sodium into erythrocytes obtained from untreated diabetics was investigated but no abnormality was found. *Seneviratne & Peiris* (205) proposed that the mechanism responsible for the abnormality involved a change in the permeability of the basal membrane which encircles the nodes of *Ranvier* and the Schwann cells which prevent a surface concentration of potassium sufficient to produce a depolarization block.

Christensen & Ørskov (39) demonstrated that the abnormality of ischaemic nerves is not confined to diabetic patients as exactly the same abnormality can be demonstrated in a large proportion of uraemic subjects. Nineteen young patients with chronic renal failure were studied, 16 of whom showed a clearly abnor

Chapter 4

THE SIGNIFICANCE OF METABOLIC STATUS

It is accepted by almost every student of diabetes that the development of diabetic angiopathy and neuropathy (in the sense of loss of reflexes, increased vibratory perception threshold, pain and paraesthesiaes) is dependent on the duration of the disease. Signs and symptoms of angiopathy and neuropathy begin to appear in some patients who have had diabetes from five to 10 years and after 15 to 25 years angiopathy and neuropathy can be demonstrated in most patients.

A number of paradoxes have appeared some of which have been explained.

Diabetic angiopathy is sometimes present at the time of diagnosis of the diabetic state. Such patients are, however nearly always old and have a mild diabetes mellitus, the time of onset of which is often very difficult or impossible to determine (136) A number of authors have reported functional and morphological alterations in prediabetics (31 126 212) The results of these studies have, however been questioned (93 141 147 179) It was mentioned earlier that the clinical manifestations of diabetic gangrene as well as coronary occlusion were to some extent dependent on the age of the patient. Thus, the clinical development of these types of angiopathy is different from that of retinopathy for instance However we now know that young patients with long-term diabetes have in fact considerable impairment of vascular function, in both the heart (107) and the extremities (36 40)

The degree of metabolic alteration in diabetics as judged by the level of the blood sugar is not worse in long-term diabetics than in patients with a recently diagnosed diabetes. Still there is ample evidence indicating that angiopathy and neuropathy are caused by the long-standing metabolic disturbances which are present despite treatment with insulin (142)

The possible relationship between metabolic status and nervous and vascular disorders can be discussed from two points of view

1 To what extent does strict regulation of the metabolic state over the course of several years protect against the development of the manifestations of long-term diabetes? There are variants of this question, e g. we may ask about the significance of strict regulation during the first few years after the diagnosis has been made or about the possibility of influencing the progression of retinopathy In these cases the time factor concerned is in the order of months to years.

2 It was stated in the beginning of this chapter that the presence of diabetic angiopathy and neuropathy was correlated to the duration of diabetes. It must be added, however that a number of disturbances or alterations in nerve and vessel function are present already at the time of clinical appearance of diabetes and that these abnormalities disappear after institution of therapy although treatment often has to be effectuated to a degree which can only be achieved in a clinical-investigative setting.

None of the abnormalities to be described and discussed in the present chapter are of any immediate significance to patients. They

are, however of considerable theoretical interest.

For practical reasons the various abnormalities have been divided into two main groups 1) nervous abnormalities and 2) vascular abnormalities.

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Christensen & Ørskov (39) demonstrated that the abnormality of ischaemic nerves is not confined to diabetic patients as exactly the same abnormality can be demonstrated in a large proportion of uraemic subjects. Nineteen young patients with chronic renal failure were studied, 16 of whom showed a clearly abnor

mal pattern similar to that found in diabetic patients. Evidence was presented which ruled out the possibility that the presence of the ischaemic phenomenon in uraemic patients was caused by the slight impairment of glucose tolerance often present in uraemic patients. The abnormality of the nerves during ischaemia was present in several uraemic patients in whom glucose tolerance was normal as judged by oral as well as intravenous tests. Furthermore, the phenomenon was not found in young subjects with glucose-tolerance-test diabetes with an impairment of glucose tolerance comparable to that found in the uraemics. No correlation was obtained between the concentration of various blood electrolytes in the uraemic patients and the threshold values obtained. *Christensen & Ørskov* (39) proposed that the retained ability to transmit sensory information during ischaemia in the diabetic and uraemic patients was due to a widespread, although not necessarily extensive, paranodal or internodal demyelination of the nerves. During ischaemia the resting membrane potential and action potential of the nerves decrease to a point where conduction is no longer possible. The abnormally prolonged preservation of sensory and motor conduction observed in the diabetics and uraemics during ischaemia is thought to be due to a facilitation of conduction produced by focal areas of demyelination which reduce the saltatory distances by acting as new points of depolarization. According to this hypothesis it is not necessary to assume that the resting membrane potential decreases at a slower rate during anoxia in diabetics than in non-diabetics.

Normalization of the vibratory perception pattern during intensive treatment with insulin is believed to be due to remyelination (39). It is obvious, however, that a normal response can be obtained when remyelination of only a small part of the nerve fiber has occurred as this area will stop the saltatory impulse at the same time as would a fully remyelinated nerve fiber.

This possibility was examined by *Terkildsen & Christensen* (225). Vibratory perception threshold was measured in the big toe and the occlusion cuff was placed above the knee or at the level of the ankle. During insulin treatment when the vibratory perception threshold of a diabetic was just normalized employing an arterial cuff placed above the knee, the results obtained on the same day with the cuff placed around the ankle were invariably abnormal. These observations are therefore in accordance with the morphological explanation offered above.

Terkildsen & Christensen (225) demonstrated that normalization of nervous function during treatment with insulin is not fully achieved everywhere along the nerve fiber at the same time. The distal parts of the nerves are more severely affected. The findings cannot be explained by a difference in length of the nerve fibers included in the two measurements, i. e. that as originally proposed (39) the longer segment will have a greater statistical chance of containing an entirely normalized part. The distance from the toe to the ankle is approximately one third of the distance from the toe to the knee, and consequently normal responses should have been obtained simultaneously approximately every third time. *Terkildsen & Christensen* (225) found that the vibratory perception threshold response to ischaemia with the cuff in the distal position was always abnormal when a normal response was elicited with the cuff placed at more proximal levels. This was also the case in a few patients with pernicious anaemia (*Christensen & Ørskov* unpublished observation) studied before and after treatment with vitamin B12 as well as in a few diabetics where the same type of experiments were performed in the upper extremity.

The reason for this is not clear. Perhaps repair occurs at a greater rate in the proximal parts of the nerves. Animal experiments (146) indicate that the ability to synthesize myelin lipids is greater in the proximal parts of the nerves. Another possible explanation is that regeneration in the foot is inhibited because of

mechanical pressure on the nerves (99) It is unlikely however that this can be the sole explanation as we have obtained results identical to those presented here when the vibratory perception threshold pattern was measured in the finger and the arterial occlusion cuff placed either above the antecubital space or at the level of the wrist. So far we have not studied the time required to normalize the vibratory perception threshold pattern when measured with the cuff placed at the level of the ankle. It is of course possible that recovery occurs at a slower rate in the foot than in the hand.

It is worthy of note that both the early reversible nervous disorders discussed here and the pathological changes in the nerves in long-term diabetics are most severe in the distal parts of the nerves.

The hypothesis that the abnormalities of ischaemic nerves are due to a defective myelin sheath not only explains the last two observations (225) but also accounts for the presence of the same abnormalities in patients with uraemia (39) and in patients with pernicious anaemia (*Christensen & Ørskov* unpublished observation) as demyelination of the nerves is a prominent morphological feature in these two conditions. The morphological explanation is also in accordance with the fact that young diabetics with recently diagnosed and untreated diabetes show a reduced motor conduction velocity which can, at least partially be normalized by treatment with insulin (87) *Seneviratne & Peiris* (205) have recently demonstrated that conduction during anoxia is preserved longer in nerves isolated from alloxan-diabetic rats than nerves from non-diabetic rats. These investigators studied the morphological picture of the nerves from the alloxan-diabetic rats and found conspicious widening of the nodal gap and fragmentation of myelin in the internodal region. Furthermore *Eliasson* (63) has recently shown that the resistance of the internodal segment is considerably reduced in nerve preparations from alloxan-diabetic rats. No information is available on the morphology of the myelin sheath in young diabetics with recently diagnosed diabetes.

Christensen & Ørskov (39) suggested the possibility that the ischaemic phenomenon might also be found in conditions other than diabetes and uraemia where demyelination of the nerves is present. At present only a few patients with pernicious anaemia have been examined. The abnormality was found in untreated patients, as mentioned above, and disappeared after treatment with vitamin B12. In one patient the abnormality could be demonstrated only with the ankle technique. This technique should preferentially be used in searching for the abnormality in other demyelinating conditions. The ischaemic abnormality has also been noted in a few long-term diabetics who had been hypophysectomized because of diabetic retinopathy but not in patients with acromegaly (*Christensen*, unpublished)

One study indicates that the abnormality of ischaemic nerves is not infrequently found in very old but apparently healthy subjects (55)

Very recently the phenomenon has been demonstrated in patients with prolonged hypercalcaemia, whereas it was not found in two patients with *Charcot-Marie-Tooth*'s disease (89)

So far only functional changes of ischaemic nerves have been discussed *Gregersen* (87) studied motor conduction velocity in diabetics with recently diagnosed diabetes. Insulin treatment was accompanied by improvement in the conduction velocity This finding has been confirmed by *Ward et al* (234)

Autonomic neuropathy has as yet never been demonstrated at this early stage of the disease (40)

VASCULAR ABNORMALITIES

The vascular abnormalities will be considered under the following headings 1) Rubeosis faciei 2) Venous dilatation in the retina and the

conjunctiva 3) Renal alterations 4) Resting blood flow in the forearm and in adipose tissue 5) Reactive hyperaemia in the forearm 6) Heart function and blood pressure.

1) Rubeosis faciei

It is generally recognized that diabetic patients tend to have pink faces. *Von Noorden* (171) noted that this condition disappeared on improvement in the diabetic state. *Lundbæk* (134) found rubeosis faciei in approximately 50 per cent of 163 long-term diabetics. In this group with a duration of diabetes between 15 and 25 years, he was not able to demonstrate any relationship between this so-called rubeosis faciei and the duration of diabetes. Probably two different types of facial redness exist in diabetics. A facial flushing seen in diabetics with ketosis and a more permanent facial redness present in many fairly well-controlled diabetics. It is not known whether the change in facial colour is due to an increase in blood flow in the skin or to an increased blood volume, but skin blood flow can be measured by ^{133}xenon employing the epicutaneous labelling technique (201) Permanent facial redness could also be caused by atrophy of cutaneous tissue

2) Venous dilatation

Rees et al (189) measured the maximal diameter of veins and arteries in the bulbar conjunctiva and found that the ratio between these two parameters was increased in newly diagnosed diabetics. According to these authors the V/A ratio became normal when these patients were treated with insulin The same abnormality was alleged to exist in prediabetics in whom the blood sugar is normal. The results obtained in prediabetics were, however later withdrawn (147) Furthermore, *Ditzel Beaven & Renold* (56) were not able to influence venous dilatation in the conjunctival beds of diabetics by discontinuance of insulin treatment.

Larsen (122) and *Jutte* (106) were both of the opinion that dilatation of the retinal veins was to some degree associated with an uncontrolled diabetic state The opinion of these authors was not based on measurements of the diameters of the vessels but upon a general impression of the calibre of the retina veins.

Skovborg et al (213) measured the diameter of veins and arteries in the retina in a large number of diabetics and non-diabetics. These investigators did not consider venous dilatation to be an early phenomenon in the development of diabetic retinopathy

Thus, there is no established correlation between venous dilatation in the conjunctiva and retina and the metabolic state.

3) Renal alterations

Stalder Schmid & Wolff (216) summarized previous investigations in this field and reported that the glomerular filtration rate was increased in young diabetics with a short duration of the disease and even in patients with recently diagnosed diabetes. Renal blood flow was not found to be consistently elevated in the diabetics, but serial determinations indicated that spontaneous variability in renal blood flow was increased. Maximal tubular phosphate reabsorption was found to be significantly higher in the diabetics.

In short-term diabetics high filtration rates were also found by *Ditzel & Schwartz* (57) and by *Mogensen* (160) *Mogensen* (160) was able to show that the abnormality was reversible during strict insulin treatment. This author (160) also determined glomerular permeability employing dextran. The clearance of a wide range of molecular weights of dextran was measured. In patients with a high glomerular filtration an increase in dextran clearance was found corresponding to the magnitude of glomerular filtration, i.e. no selective alterations in permeability were present.

Mogensen (160) has recently proposed that the increased filtration rate in juvenile diabetics might be explained by elevated plasma growth hormone levels. He has demonstrated

a fairly good correlation between plasma growth hormone levels and the glomerular filtration rate in a group of juvenile diabetics studied before and during a long period of intensive insulin treatment. The change in glomerular function is, however, not quite identical to that seen after the administration of growth hormone (52) because the renal plasma flow is not elevated in diabetes of recent onset.

4) Resting blood flow in forearm and in adipose tissue

Christensen (42) studied resting forearm blood flow employing classical venous occlusion plethysmography in 11 young diabetics and in seven non-diabetics. The diabetics were studied before treatment with insulin or after withdrawal of treatment and again two to 26 days after institution of therapy. Resting blood flow was approximately doubled in the untreated diabetics compared to normal controls. A slight but significant decrease in resting blood flow took place during insulin treatment, but the resting flow in the treated diabetics still exceeded that of the controls. This finding of an increased resting blood flow in the good to fairly well-controlled diabetics is unexpected. In studies of resting blood flow in the anterior tibial muscle and in the foot (36, 40) the mean resting blood flow was the same in diabetics and controls.

Butterfield & Whichelow (30) noted a high resting blood flow in the forearm in a group of juvenile diabetics with a duration of the disease between seven and 12 years. *Alexander Teusen & Mitzkat* (7) also found elevated resting blood flow values in various parts of the extremities in diabetics, although the increase was very small. In neither of these two studies was the significance of the metabolic status discussed.

Increased blood flow has also been reported in adipose tissue in untreated diabetics (103). Insulin administration is accompanied by a decrease

5) Reactive hyperaemia in the forearm

Christensen (42) studied reactive hyperaemia in the forearm in 11 juvenile diabetics and in seven control subjects before insulin treatment or after withdrawal of treatment and again after institution of therapy. Peak flow was found to be higher in the diabetics than in the normal controls, but no difference was obtained before and after treatment with insulin. Particular attention was paid to the restoration phase of the hyperaemic period, i. e. the rate of return of blood flow towards basal levels after the initial hyperaemia. The speed of recovery was expressed as the *half time*. The half time was considerably increased in the untreated diabetic patients and correlated with total plasma CO_2. The abnormality disappeared after treatment with insulin. Evidence was presented which indicated that the abnormality was not due to changes in pH, pCO_2 or bicarbonate, per se. Dehydration was also excluded as a causal factor. The observed increase in resting blood flow in untreated diabetics discussed above and the prolongation of the recovery phase are similar to the alterations described by others in non-diabetics after infusion of adrenaline or depletion of the noradrenaline stores by reserpine (3, 59). *Christensen* measured (42) the urinary excretion of catecholamines in a few diabetic patients in whom the half time was prolonged and the results compared with values obtained in a larger group of normal subjects. No tendency to increased adrenaline values was observed in the diabetics before starting insulin therapy and no difference whatsoever was observed between the two metabolic conditions.

Employing a sensitive and precise radio-enzymatic assay for measuring catecholamines in plasma, *Christensen* (unpublished observations) examined the possibility that catecholamines are released from the nerves in the forearm during ischaemia. Venous blood was collected before application of an arterial occlusive cuff and at the end of a 10 to 15 min period of ischaemia before release of the cuff

The catecholamine content of the venous blood did not differ under these two conditions, this was observed in non-diabetics as well as in a ketotic diabetic studied at a point of time when the recovery phase after ischaemia was considerably prolonged.

Christensen (43) has demonstrated that plasma catecholamines are elevated in ketotic juvenile diabetics. Both plasma adrenaline and noradrenaline are raised (44) Therefore, the explanation for the adrenaline-like changes in the forearm could simply be an elevated plasma adrenaline concentration. Further studies have, however not supported this point of view (48) The most consistent change in plasma catecholamines in keto-acidosis is an increased level of noradrenaline Plasma nor adrenaline seems to be elevated in all patients with keto-acidosis and increases with the degree of metabolic derangement. Very high levels of plasma adrenaline have been observed in some patients but others have shown normal values. Furthermore, elevated plasma adrenaline levels have not been observed in patients with very mild keto-acidosis in whom haemodynamic changes are clearly present. It is possible that elevated plasma adrenaline levels occur intermittently but the question has not yet been fully settled.

Gundersen (90) and *Nielsen* (170) have confirmed the observation that resting blood flow is increased and reactive hyperaemia abnormal in diabetics with keto-acidosis. Gundersen found that the resting blood flow was only significantly increased in diabetics who previously had been treated with insulin and not in subjects with recently diagnosed diabetes. Both groups of subjects showed a prolongation of the hyperaemic response The increase in the forearm blood flow is mainly due to an increase in muscle blood flow as expected (170) *Nielsen* (170) made the interesting observation that changes in forearm blood flow similar to those seen in diabetics are also present in non-diabetics during prolonged fasting, although the changes are less pronounced

The above mentioned studies indicate that the haemodynamic changes observed in diabetics with keto-acidosis are not exclusively a consequence of dehydration (42) but the mechanism of the adrenaline-like changes in the forearm deserves further investigation.

6) Heart function and blood pressure

Carlstrøm & Karlefors (32, 33) studied blood pressure measured intraarterially during exercise in a small group of non-acidotic diabetic patients before and after treatment with insulin. Systolic and diastolic pressure were found to be slightly but significantly higher in the untreated diabetics in comparison with normal controls. In addition heart rate was increased and stroke volume decreased in the untreated diabetics but the differences were not significant. Seven of the 9 diabetic patients were also examined after institution of therapy and the results compared with those obtained in the same patients before treatment. No change in intraarterial pressure could be demonstrated. In a later study (108) which included observations on 10 diabetic patients, the authors reported that heart rate was significantly lower and stroke volume significantly higher after treatment. It should be mentioned that the patients were re-examined during good control a long time after the institution of therapy perhaps after a year or more. For this reason the proposed correlation between the metabolic status and the vascular changes might be questioned.

It is well known that diabetics with precoma and coma demonstrate tachycardia. Cardiac output is probably increased (100)

In conclusion, the aforementioned studies clearly indicate that alterations in nervous and vascular function accompany changes in the metabolic status. Accordingly these changes are also present in patients with diabetes of recent onset and disappear after insulin therapy At present, the abnormality of ischaemic nerves is the most extensively studied phenom-

enon. The peculiar resistance of nervous function to anoxia is apparently confined to myelinated fibers and it is proposed that the abnormality is due to a defective myelin sheath. Glomerular filtration rate is increased in untreated diabetics and becomes normal after a period of insulin treatment. Pronounced haemodynamic alterations accompany keto-acidosis. Plasma catecholamines are considerably elevated. The circulatory changes occur in part secondarily to dehydration. In the forearm, however adrenaline-like circulatory changes are consistently observed. It is very unlikely that these changes occur secondarily to dehydration and they are probably a more direct result of the metabolic derangement, but the mechanism has not been elucidated

There is no obvious relationship between the reversible vascular disturbances and the vascular disease seen in long term diabetics. The vascular disease in diabetes of long standing probably depends on morphological changes in large and small vessels. A connection might, however exist between the earliest nervous disturbances and diabetic neuropathy

SUMMARY

Chapter 1

By way of introduction the object of the survey is defined: to present a summary, a discussion, and an estimate of the available functional investigations of diabetic angiopathy and neuropathy, principally those confined to the extremities. The functional examinations reviewed fall into three main categories: a) circulation and autonomic nervous function in long-term diabetes (chapter 2), b) capillary resistance and capillary permeability in long-term diabetes (chapter 3), and c) the influence of the metabolic status on vessel and nerve function (chapter 4).

The introductory chapter (chapter 1) deals rather briefly with clinical, radiological and morphological examinations of the extremities.

Clinical investigations indicate that ulceration and gangrene of the lower extremities occur more frequently in diabetics than in non-diabetics. The presence of gangrene in diabetes is, however, to some degree dependent on the age of the patients and clinical vascular disease is seldom found in young long-term diabetics and not at all with the same frequency as clinically significant retinopathy. The cause of diabetic gangrene is a controversial issue. Most authors stress the importance of a vascular disease, the nature of which is in dispute, while some investigators emphasize the importance of diabetic neuropathy.

Radiological examinations have quite unequivocally shown that calcification of the arteries in the lower extremities occurs much more frequently in diabetics than in non-diabetics. The calcification is located to the tunica media of the arteries. This abnormality is found even in young diabetics and it is correlated to the duration of diabetes. Calcification of the media is also found in non-diabetics in old age, but it is generally considered to be a rather innocent abnormality not connected to clinical vascular disease. Only a few arteriographic investigations of the vessels of the extremities in diabetics with manifest vascular disease have been published. The results indicate that the distal arteries are more often the site of occlusive changes in diabetics than in non-diabetics.

Some investigators have not been able to show any differences in either the distribution or the morphology of the arterial disease in diabetics and in non-diabetics with occlusive vascular disease. Other investigators stress, however, in agreement with the results of the above mentioned radiological examinations, that occlusive disease is much more frequently found in the distal arteries in diabetes and that calcification of the media is more widespread. A single study reports a correlation between the presence of calcification of the media and the finding of fibrosis of the intima. It is generally accepted that in diabetics morphological changes are often found in the small vessels, the arterioles and the capillaries. The walls of the arterioles are thickened because of the accumulation of a PAS-positive material and the basement membrane of the

capillaries is also thickened. These changes seem to be patchy. Some authors propose that these changes of the small vessels are an important factor in the development of diabetic gangrene and neuropathy but the morphological evidence for this hypothesis is disputed.

Finally it is emphasized that functional investigations of the circulation in the extremities may give more information about the vascular disease of diabetes.

Chapter 2

Chapter 2 deals with the circulation and autonomic nervous function in long-term diabetes. The information available in the literature is to a high degree contradictory and confusing. Thus some investigators seem to have found a reduction in vascular function in patients with a very short duration of diabetes and without other signs of diabetic angiopathy whereas others have reported that the parameters of vascular function are quite normal in long-term diabetics. Two factors in particular seem to be responsible for these divergences: firstly the use of unreliable methods for the evaluation of blood flow and secondly a misinterpretation of the results obtained after nerve block.

The author's own investigations have shown that maximal blood flow measured by radioactive xenon in the tibialis anterior muscle decreases with increasing duration of diabetes (on the average 1 per cent of the normal value for each year of disease). A closer analysis of the results shows that a reduction in blood flow is confined to long-term diabetics with arterial calcification of the tunica media, whereas diabetics without calcification have normal values for blood flow irrespective of the duration of the disease. Measurements of reactive hyperaemia in the foot employing classical venous occlusion plethysmography also demonstrate a decrease in peak flow with increasing duration of diabetes (about 2 per cent per year of disease).

With a s[ingle ex]ception a reduced peak flow wa[s] fo[und] on[ly] in patients with widespread art[erial calci]fication of the vessels. In the [...] [re]duction in blood flow in the low[er legs] of long term diabetics must be [an i]mportant factor for the development [of diabet]ic gangrene. The established [...] reduced blood flow and [...] [arte]rial medial calcification [...] [res]ults of the aforementioned [...] morphological examinations of [...] [vess]els of the extremities indicate that [the v]ascular disease in juvenile diabetes is in som[e r]espects different from the form of atherosclerosis found in non-diabetics of comparable age.

The duration of diabetes does not influence the magnitude of the resting blood flow but many long-term diabetics demonstrate a considerable reduction or a total lack of the so-called spontaneous variations of resting blood flow. Several investigators have previously shown that the skin temperature of the extremities does not rise during indirect heating in patients who have had diabetes for many years. The existence of these neurovascular abnormalities is in the main a manifestation of autonomic neuropathy. Reduced function of the vessels per se may also contribute to their presence.

It has been known for several years that the blood vessels of diabetics are hypersensitive to adrenaline. This abnormality is probably due to an autonomic neuropathy, i.e. a reduced axonal uptake and inactivation of the catecholamines.

The author has studied the correlation between the degree of diabetic neuropathy (the threshold of vibration sense) and the vascular disease (peak flow). No correlation was found, however between these two parameters. It is emphasized that it is unlikely that ischaemia is of any major importance in the development of diabetic neuropathy.

Finally there is a brief summary of earlier investigations of arterial rigidity and the regulation of blood pressure in diabetes.

Chapter 3

Chapter 3 deals with capillary resistance and capillary permeability in long-term diabetes. It is well known that skin capillary resistance is reduced in long term diabetics. This abnormality is found in patients with retinopathy and is correlated to the degree of retinal damage. The cause of the reduced capillary resistance is unknown but may be found in the earlier mentioned morphological changes of the small vessels. A reduced concentration of acid mucopolysaccharides in and about the vascular wall might also be of significance. The reduced capillary resistance is not caused by high blood pressure, but an elevated blood pressure may be a contributary factor in some patients.

Within the last few years several investigators have studied capillary permeability in diabetes. Fluorescein angiography of the retina and iris have revealed that the capillary walls are permeable to the dye in diabetics with retinopathy. Capillary permeability to small ions is increased in muscles in such patients. The proteinuria of diabetic nephropathy is not, however, caused by an increased permeability of the fenestrated capillaries of the glomeruli.

It is now known that hypophysectomy slows down the progression of diabetic retinopathy and visual impairment. The author has found that skin capillary resistance becomes normal in hypophysectomized patients. Quantitative measurements have shown that the capillary resistance in hypophysectomized patients is often above that of normal individuals. A similar increase in retinal capillary resistance could be one of the factors responsible for the effect of pituitary ablation on diabetic retinopathy. Fluorescein angiographic examinations of the retina have shown that the abnormal leakage of dye ceases shortly after hypophysectomy. Whereas long term diabetics demonstrate a reduced capillary resistance and an increased capillary permeability, hypophysectomy seems to normalize these conditions.

It has not been clarified by which mechanism hypophysectomy influences capillary resistance and capillary permeability. The changes may be caused by a pronounced vasoconstriction mediated to some degree by the sympathetic nervous system. Abolition of growth hormone secretion after hypophysectomy is probably the primary cause of the changes in capillary resistance.

Chapter 4

Chapter 4 covers the influence of the metabolic status on vascular and nervous function. It is generally accepted that diabetic angiopathy and neuropathy develop over a number of years. After five to 10 years of diabetes the first signs of the disease appear and after 15 to 25 years angiopathy and neuropathy can be demonstrated in most diabetics. It must be added, however, that a number of abnormalities in nervous and vascular function are present already at the time of clinical appearance of diabetes. These changes will disappear in days to weeks provided the diabetic patient is treated intensively with insulin. The functional disturbances fall into two main groups a) nervous, b) vascular.

About 10 years ago it was shown that nervous transmission is retained significantly better during ischaemia in patients with a recently diagnosed and untreated diabetes than in normals. This is most easily demonstrated by measuring the threshold of vibratory perception on the big toe, the ischaemia being induced by inflating a cuff placed just above the knee. Vibratory sensation disappears completely in healthy subjects after approximately 20 minutes, whereas diabetics retain perception unchanged or slightly reduced for at least 30 minutes. On careful treatment with diet and insulin perception becomes normal in the course of two to three weeks. The phenomenon is not unique to diabetes, as it is also found in uraemia, probably in pernicious anaemia, and in very old but otherwise healthy persons. The ischaemic abnormality is most

pronounced in the distal parts of the nerves just like the neuropathy of long-term diabetes. The cause of the abnormally high resistance of the diabetic nerve fibers to anoxia is not known. It is possible that the abnormality is confined to myelinated nerve fibers. The abnormality is certainly due to changes in the nerve fibers and not in the peripheral sensory receptors. The author is of the opinion that the abnormality of ischaemic nerves in diabetes is caused by a defective myelin sheath. Functional disturbances are also found in non-ischaemic nerves in patients with a recently diagnosed diabetes. Thus motor conduction velocity is reduced, and insulin treatment is accompanied by improvement in conduction velocity

The following vascular abnormalities are discussed a) rubeosis faciei b) venous dilatation of retina and conjunctiva c) glomerular filtration rate d) resting blood flow of muscle and fat tissue e) reactive hyperaemia in the forearm f) heart function and blood pressure.

It has not been proved that dilatation of the veins of the conjunctiva and retina are found more frequently in untreated diabetics than in well treated patients. It is well established that the glomerular filtration rate is increased in patients with newly diagnosed diabetes and that it becomes normal after a period of careful insulin treatment. The abnormality is not due to an increase in glomerular capillary permeability and the cause remains unknown. Pronounced haemodynamic alterations accompany ketoacidosis in diabetics. Plasma catecholamine concentrations are considerably elevated. Circulatory changes are partly secondary to dehydration. In the forearm, however adrenalinelike circulatory changes are consistently observed. The resting blood flow is increased and the hyperaemic period after ischaemia is prolonged. It is very unlikely that these changes occur because of dehydration and they are probably a more direct consequence of the metabolic derangement.

REFERENCES

1 Aagenaes, Ø. & Moe, H. Diabetes *10* 253 1961
2. Aagenaes, Ø. Rep. Steno Hosp. *11* 7 1963
3 Abrams, M. E., Barker D J P & Butterfield, W J H. Clin. Sci. *29* 565 1965
4 Abramson. D I & Katzenstein, K. H Amer Heart. J *21* 191 1941
5 Abramson, D L. Circulation in the Extremities. London 1967 page 78
6. Alexander K., Nissen, P & Mitzkat, H. J Angiologica *4* 95 1967
7 Alexander K., Tensen, R. & Mitzkat, H J Klin. Wschr *46* 234 1968
8. Alpert, J S., Coffman, J D Konez, L., Balodimos, M. & Soeldner J S. Clin. Res. *18* 449 1970.
9 Baggesen, L. H Acta ophthal. *47* 449 1969
10. Balodimos, M. C., Rees, S. B., Aiello, L. M Bradley R. F & Marble, A. in (ed. Goldberg, M. F & Fine, S. L.) Symposium on the Treatment of Diabetic Retinopathy Public Health Service Publication No. 1890 Washington 1969 page 153
11 Banson, B. B. & Lacy P E. Amer J Path. *45* 41 1964.
12. Barany F R. Acta med. scand. Suppl. 304 1955
13 Barany F R. & Cooper E. H. Clin. Sci. *15* 533 1956.
14 Barcroft, H Brit. med. Bull. *8* 363, 1952.
15 Barcroft, H & S an, H. J C. Sympathetic Control of Human Blood Vessels. London 1953
16. Barner H B Kaiser G C. & Willman, V L. Circulation *43* 391 1971
17 Barnes, R. H Amer J Med Sci. *219* 368, 1950.
18. Beaser S. B., Rudy A. & Seligman, A. M Arch. Intern. Med. 73 18, 1944
19 Bell, E. T Arch Path *49* 469 1950
20. Bell. E. T Amer J clin. Path *28* 27 1957
21 Berkson, J Biomet Bull *2* 47 1946
22 Berner J H J Acta med scand *143* 336, 19 2
23 Berry R. E. L. & Flotte, C. T Arch. Surg. *71* 460, 1955
24 Blumenthal, H T Lansing, A. L & Wheeler P A. Amer J Path. *20* 665 1944
25 Bojs, G Falkheden, T Sjøgren, B & Varnauskas, E. Acta Endocr *39* 308, 1962.
26 Brodie, T G & Russell, A. E. J Physiol. *32* xlvii, 1905
27 Bryfogle, J W & Bradley R. F Diabetes *6* 159 1957
28. Burch, G E. Proc. Soc. exp. Biol. (N Y) *102* 400, 1959
29 Burton, A. C. Amer J Physiol. *127* 437 1939
30. Butterfield, W J H & Whichelow M. J Diabetologia *1* 43 1965
31 Camerini-Davalos, R. A. Med. Clin. N Amer *49* 865 1965
32. Carlstrøm, S. & Karlefors, T Acta med. scand. *181* 759 1967
33 Carlstrøm, S. & Karlefors, T Acta med. scand. *181* 747 1967
34. Castaigne, P Cathala, H P Dry J & Mastropaolo, C. Rev neurol. *115* 61 1966
35 Chopra, I S., Hurwitz, L. I & Montgomery D A. D Brain *92* 391 1969
36. Christensen, N J Acta med. scand. *183* 449 1968
37 Christensen, N J Acta med. scand. *183* 445 1968.
38. Christensen, N J Lancet *2* 1270, 1968.
39 Christensen, N J & Ørskov H. J Neurol. Neurosurg. Psychiat. *32* 519 1969
40. Christensen, N. J Diabetologia *5* 171 1969
41 Christensen, N J Acta med. scand. *185* 553 1969
42. Christensen, N J Clin. Sci. *39* 539 1970.
43 Christensen, N J Scand. J clin. Lab Invest. *26* 343 1970.
44 Christensen, N J Scand. J clin. Lab. Invest. *27* 227 1971
45 Christensen, N J & Terkildsen, A. B. Diabetes *20* 297 1971

46. Christensen, N J In: Blood Vessel Disease in Diabetes Mellitus (eds., K. Lundbæk and H Keen). Acta Diabetologica Latina (5 Capri Conference) *8* suppl. 1 1971 page 203
47 Christensen, N J J lin. Invest. *51* 779 1972.
48. Christensen, N J In: Neuro and Vascular Changes in Early Diabetes (II International Symposium on Early Diabetes). Curacao 1971 In print.
49 Christensen, N J Diabetologia (abstract). In print.
50. Cometta, F & Cuendet, J F Bull. Soc. franc. Ophtal. *62* 237 1949
51 Conrad, M C. Circulation *36* 83 1967
52. Corvilain, J & Abramow M J lin. Invest. *41* 1230, 1962.
53 Deckert, T & Poulsen, J E. Acta med. scand. *183* 351 1968.
54. Dietrich, K. Virchows Arch. path. Anat. *274* 452, 1930.
55 Digiesi, V Malavasi, A. & Giraudi, D Rass. Neurol. veg. *23* 1 1969
56. Ditzel, J Beaven, D & Renold, A E. Metabolism *9* 400, 1960.
57 Ditzel, J & Schwartz, M Diabetes *16* 264 1967
58. Dolman, C. L. Neurology *13* 135 1963
59 Dornhorst, A. C. & Whelan, R. F Clin. Sci. *12* 33, 1953
60. Doupe, J J Neurol. Neurosurg. Psychiat. *6* 97 1943
61 Dry T J & Hines, E. A. Ann. intern. Med. *14* 1893 1941
62. Duff R. S. & Swan, H. J C. J Physiol. *114* 41 1951
63 Ellenson, S. G J Neurol. Neurosurg. Psychiat. *32* 525 1969
64. Fagerberg, S.-E. Acta med. scand. Suppl. 345 1959
65 Feinberg, A. W & Lax, H. J Amer med. Ass. *201* 105 1967
66. Felder D Russ, E., Montgomery H & Horwitz, O Clin. Sci. *13* 251 1954
67 Ferrier T M Aust. Ann. Med. *13* 222, 1964
68. Ferrier T M Med. J Aust. *1* 5 1967
69 Foxworthy L. R. Cit. by W pener H P in Proc. Amer Diab. Ass *5* 201 1945
70. Freeman, N E. Amer J Physiol. *113* 384, 1935
71 Friederici, H. H R., Tucker W R. & Schwartz, T B Diabetes *15* _33 1966.
72. Fuenl, H. U Schweiz. med. Wschr *95* 487 1965
73 G bbay K. H., Merola, L. O & Field, R. A. Science *151* 209 1966.
74. Gandolfi, C. G Ital. oftal. *3* 321 1950.
75 Gensler S. W Halmovici, H Hoffert, P Steiman, C. & Beneventano, T C. Arch. Surg. *91* 617 1965
76. Getz, O S., Vesselinovitch, D & Whaler R W Amer J Med. *46* 657 1969
77 Goldenberg, S Alex, M., Joshi, R. A. & Blumenthal, H. T Diabetes *8* 761 1959
78. Golenhofen, K. In: Circulation in Skeletal Muscle (Ed. O Hudlicka). Pergamon Press, 1968. Page _87
79 Goodman, J I. et al. The Diabetic Neuropathies. Springfield, Ill., 1953.
80. Goodman, J I Amer J Med. *41* 831 1966.
81 Gough, K. R. Brit. med *J 1* 1 1962.
82. Graettinger J S., Muenster J J Checchia, C. S., Grissom, R. L. & Campbell, J A. J clin. Invest. *37* 502, 1958.
83 Greenbaum, D Richardson, P C. Salmon, M. V & Urich, H. Brain *87* 201 1964
84 Greenfield, A. D M Shepherd, J T & Whelan, R. F J Physiol. *112* 459 1951
85 Greenfield, A. D M. Brit. med. Bull. *19* 101 1963
86. Gregersen, G J Neurol. Neurosurg. Psychiat. *31* 175 1968.
87 Gregersen, G. Diabetologia *4* 273 1968.
88. Gregersen, G Perifere nervers funktion ved diabetes mellitus. Thesis, Arhus 1969
89 Gregersen, G & Pilgaard, S. Acta neurol. scand. *47* 71 1971
90. Gundersen, H J Prize paper Aarhus University 1971
91 Handelsman, M B., Levitt, L. M & Conrad, H J Amer J med. Sci. *2* 4 34 1952.
92. Hansen, J Acta med scand. *183* 553 1968.
93 Hansen, R. Ø Diabetologia *1* 97 1965
94. Hansum, S Acta Ophthal. Suppl. 16, 1939
95 Hart, A. & Cohen, H Brit. med. J *1* 89 1969
96. Hertting, G Axelrod, J Kopin, I J & Whitby L. G Nature *189* 66, 1961
97 Hevelke G. Z. Alternsforsch. *9* 28, 1955
98. Hines, E. A. & Barker N. W Amer J med. Sci. *200* 717 1940.
99 Hopkins, A. P Morgan-Hughes, J A. J Physiol. *189* 81 P 1967
100. Howarth, S McMichael, J & Sharpey-Schafer E. P Clin. Sci. *6* 247 1948
101 Hunter P R., Bloom, A., Kelsey J H. & Porter R. Diabetologia *7* 20 1971
102. Huston, J H. & Abboud, F M. Circulation *25* 938, 1962.
103 Häggendal, E., Steen, B. & Svanborg, A. Acta med. scand. *187* 49 1970
104. Ismail, A. A., Khalifa, K. & Madwar K. R. Lancet *2* 810, 1965

105 Jensen, V A. & Lundbæk, K. Diabetologia *4* 161 1968.
106. Jilte, A. In: Diabetische Angiopathie (Ed. G Mohnike). Abhandlungen der deutschen akademie der wissenschaften zu Berlin. Klasse für Medizin. Nr 3 Berlin 1964 Page 13.
107 Karlefors, T Acta. med. scand. *180* suppl. 449 1966.
108 Karlefors, T & Carlstrom, S. Brit. Heart J *32* 355 1970
109 Keen, H., Rose, G Pyke, D A., Boyns, D Chlouverakis, C. & Mistry S. Lancet *2* 505 1965
110. Keen, H Chlouverakis, C., Jarrett, R. J & Boyns, D R. Postgrad. med. J Suppl. 5 960, 1968.
111 Kelly P J & Coventry M B J Amer med. Ass. *168* 388, 1958.
112. Kety S S. Amer Heart J *38* 321 1949
113. Kingsbury K. J Lancet *2* 1374, 1966.
114. Kingsbury K. J Postgrad. med. J Suppl. 5 944, 1968.
115. Kingsbury K. J N ture *224* 146, 1969
116. Kornerup, T Acta Ophthal. 33, 583 1955
117 Kramer J Meyers, V W McCarthy H. H. & Simay Kramar M. Endocrinology *60* 589 1957
118. Kramer D W Amer J med. Sci. *183* 503 1932.
119 Kramer D W Diabetes *7* 384 1958.
120. Labbe, M. & Lenfantin, H Bull. Soc. med. Hop. Paris *48* 522, 1924
121 Langer L., Bergentz, S. E., Bjure, J & Fagerberg, S. E. Diabetologia *7* 29 1971
122. Larsen, H. W Rep Steno Hosp. *10* 7 1961
123 Lassen, N A., Lindbjerg, J & Munck, O. Lancet *1* 686, 1964
124 Lassen, N A. J clin. Invest. *43* 1805 1964
125 Lax, H. & Feinberg, A. W J chron. Dis. *3* 618, 1956.
126. Lax, H & Feinberg, A. W Circulation *20* 1106, 1959
127 LeFevre F A Corbacioglu, C., Humphries, A. W & deWolfe, W G J Amer med. Ass. *170* 656, 1959
128. Leutenegger F Z. klin. Med. *119* 164 1931
129 Lindbjerg, L F Xenon-133 in the Study of Peripheral Circulation in Obliterative Arterial Disease Thesis, Copenhagen: Munksgaard 1969
130 Lindbom. A. Acta radiol. (Stockh.) Suppl. 80, 1950
131 Lisa, J R., Magiday M & Hart, J F J Amer med Ass *118* 1353 1942
13 Lobstein, J-G-C F M T ites d'Anatomie pathologique. Paris Levrault 1829
133 Lopez Majano, V Rhodes, B. A. & Wagner H N. Jr J appl. Physiol. *27* 782, 1969
134 Lundbæk, K., Long-term Diabetes. Copenhagen: Munksgaard 1953
135 Lundbæk, K. Lancet *1* 377 1954
136 Lundbæk, K. Acta med. scand. *152* 53, 1955
137 Lundbæk, K., Malmros, R., Andersen, H C., Ohrt, V & Jensen, V A. Diabetes *11* 474, 196..
138 Lundbæk, K. Nord. Med. *78* 946, 1967
139 Lundbæk, K., Malmros, R., Andersen, H C., Rasmussen, J H Brunse, E., Madsen, P H. & Jensen, V A. In (ed. Goldberg, M F & Fine, S. L.) Symposium on the Treatment of Diabetic Retinopathy Public Health Service Publication No. 1890 Washington 1969 page 291
140. Lundbæk, K., Christensen, N J Jensen, V A., Johansen, K., Olsen, T S., Hansen, A. P Ørskov H & Østerby R. Lancet *2* 131 1970.
141 Lundbæk, K. In Nobel Symposium 13 Pathogenesis of Diabetes Mellitus (ed. E. Cerasi & R. Luft). Uppsala 1970 (page 97).
142. Lundbæk, K., Christensen, N J Jensen, V A., Johansen, K., Olsen, T S., Hansen, A. P Ørskov H. & Østerby R. Dan. med. Bull. *18* 1 1971
143 Mainland, D Amer Heart J *45* 644, 1953
144 Malins, J Clinical Diabetes Mellitus. London 1968
145. Mallory O T Jr Proc. Amer Fed. Clin. Res. *2* 34, 1945
146. Manjo, G. & Karnovsky M. L. J exp. Med. *107* 475 1958.
147 Marble, A. Diabetes *16* 825 1967
148. Marchand, F Verh. dtsch. Kongr inn. Med. *21* 23, 1904
149 Martin, M. M. Lancet *1* 560, 1953
150. Martin, M M. Proc. roy Soc. Med. *47* 139 1954
151 McMillan, D E., Breithaupt, D L., Rosenau, W Lee, J C. & Forsham, P H. Diabetes *15* 251 1966.
152. Megibow R. S., Pollak, H., Megibow S. J Bookman, J J & Osserman, K. Amer Heart J *38* 468, 1949
153 Megibow R. S., Megibow S. J Pollak H Bookman, J J & Osserman, K. Amer J Med. *15* 322, 1953
154 Mendlowitz, M Grossman, E. B. & Alpert, S. Amer J Med. *15* 316, 1953
155 Mendlowitz, M. The Digital Circulation. New York 1954 (page 103).
156. Merimee, T J Fineberg, S. E., McKusick, V A. & Hall, J J clin. Invest. *49* 1096, 1970.
157 Mitchell, J R. A., & Schwartz, C. J Arterial Disease. Oxford 1965

158 Mogensen, C. E. Scand. J. clin. Lab. Invest. *28* 183 1971
159 Mogensen, C. E. In preparation.
160. Mogensen, C. E. Scand. J. clin. Lab. Invest. *28* 79 1971
161. Moore, J. M. & Frew I. D. O. Brit. med. J. *2* 19 1965
162. Moorhouse, J. A., Carter S. A. & Doupe, I. Brit. med. J. *1* 883, 1966.
163 Moses, C. Atherosclerosis. Philadelphia 1963
164 Munck, O. Lindbjerg, I. F. Binder C., Larsen, N. A. & Trap-Jensen, J. Diabetes *15* 323, 1966.
165 Möckeberg, J. G. Virchows Arch. path. Anat. *171* 141 1903
166. Mårtensson, J. Acta med. scand. *137* 335 1950.
167 Nathanielsz, P. W. & Ross, E. J. Diabetes *16* 462, 1967
168. Neubauer B. Prize paper Arhus University 1968.
169 Neubauer B. Diabetologia *7* 409 1971
170. Nielsen, S. L. Prize paper Aarhus University 1971
171 Noorden, C. von & Isaac, S. Die Zuckerkrankheit und ihre Behandlung. Berlin, 1927 (page 279).
172. Norn, M. S. Acta Ophthal. *45* 322, 1967
173 Oakley W. Catterall, R. C. F. & Martin, M. M. Brit. med. J. *2* 953, 1956.
174 Oakley W. G., Pyke, D. A. & Taylor K. W. Clinical Diabetes and its Biochemical Basis. Oxford and Edinburgh 1968
175 Oakley N. W. Joplin, G. F. Kohner E. M. & Fraser T. R. In (ed Goldberg, M. F. & Fine, S. L.) Symposium on the Treatment of Diabetic Retinopathy Public Health Service Publication No. 1890 Washington 1969 page 317
176 Odel, H. M., Roth, G. M. & Keating, F. R., Diabetes *4* 92, 1955
177 *Ortiz, J. M. V. Soto, C. M., Staffieri, J. J. &* Ross, J. de. Arch. Soc. oftal. hisp.-amer *9* 245 1949
178. O'Sullivan, J. B. Cosgrove, J. & McCaughan, D. Postgrad. med. J. Suppl. *5* 955, 1968.
179 Otto, H. & Mauren, A. In Fortschritte der Diabetes Forschung. 1 Symposion des Deutschen Diabetes-Komitee am 26. und 27. Oktober 1962 in Dusseldorf (Ed. Oberdisse K., & Jahnke, K.), page 164
180. Pardo, V. Perez Stable, E., Fisher E. R. Lab. Invest. *15* 1994, 1966.
181 Pedersen, J. & Olsen, S. Acta med. scand. *171* 551 1962.
182. Pickering, G. W. Amer. J. Med. *34* 7 1963
183 Popoff N. W. Arch. Path. *18* 295 1934.
184. Porstmann, W. Dtsch. Z. Verdau.-u. Stoffwechselkr *14* 87 1954
185 Post, L. T. & Stickle, A. W. Amer. J. Ophthal. *34* 1119 1951
186. Randerath, E. & Diezel, P. B., Dtsch. Arch. klin. Med. *205* 523 1959
187 Rasmussen, K. E. Acta Ophthal. *44* 641 1966.
188. Rau, G. In Kreislaufmessungen (H. Krause, ed.) page 94 Germany 1962.
189 Rees, S. B., Camerini-Davalos, R. A., Caulfield, J. B. Lozano-Castaneda, O. Cervantes-Amezcua, A., Taton, J. Pometta, D. Krauthammer J. P. & Marble, A. Ciba Foundation Colloquia on Endocrinology Diabetes mellitus, vol. 15 1964, page 315
190. Reske-Nielsen, E. & Lundbæk, K. Diabetologia *4* 34, 1968.
191 Robertson, W. B. & Strong, J. P. Lab. Invest. *18* 538, 1968.
192. Rodriguez, R. & Root, H. F. New Engl. J. Med. *238* 391 1948.
193 Rosing, N. Lancet *2* 1188, 1965
194. Rundles, R. Medicine *24* 111 1945
195 Sappington, S. W. & Horneff, J. A. Amer. J. med. Sci. *201* 862, 1941
196. Sappington, S. W. & Fischer H. R. Arch. Path. *34* 989 1942.
197 Schadt, D. C., Hines, E. A. J. Juergens, J. L. & Barker N. W. J. Amer. med. Ass. *175* 937 1961
198. Schiller S. & Dorfman, A. Biochem. biophys. Acta *78* 371 1963
199 Schroeder W. Z. ges. exp. Med. *137* 1 1963
200 Scott, D. J. Dollery C. T. Hill, D. W. Hodge, J. V. & Fraser R. Brit. med. J. *1* 811 1964
201 Sejrsen, P. J. appl. Physiol. *24* 570, 1968.
202. Selvaag, O. Atherosclerosis obliterans. A clinical study Oslo 1964
203 Semple, R. Lancet *1* 1064, 1953
204. Seneviratne, K. N. & Peiris, O. A. J. Neurol. Neurosurg. Psychiat. *31* 348, 1968.
205 Seneviratne, K. N. & Peiris, O. A. J. Neurol. Neurosurg. Psychiat. *32* 462, 1969
206. Shanes, A. M. Fed. Proc. *10* 611 1951
207 Shapiro, A. P. Moutsos, S. E. & Krifcher E. J. clin. Invest. *42* 1890, 1963
208. Sharpey Schafer E. P. & Taylor P. J. Lancet *1* 559 1960
209 Shepherd, J. T. Physiology of the Circulation in Human Limbs in Health and Disease. London 1963 (page 101)
10 Sigroth, K. Acta med. scand. Suppl. 325 1957
211 Silbert, S. & Lippmann, H. I. J. Amer. med. Ass. *151* 1176, 1953
212. Siperstein, M. D. Unger R. H. & Madison, L. L. J. clin. Invest. *47* 1973 1968

213 Skovborg, F Nielsen, Aa. V Lauritzen, E. & Hartkopp, O Diabetes *18* 292, 1969

214 Spetz, S. Acta obstet. gynec. scand. *44* suppl. 1 1965

215 Spiegelman, A. R. & Herrera, L. Diabetes *3* 220 1954

216. Stalder G Schmid R. & Wolff, M. v Dtsch. med. Wschr *85* 346, 1960.

217 Stary H C. Amer J med. Sci. *252* 357 1966.

218. Steinberg, F U & Graber A. L. Arch. phys. Med. *44* 645 1963

219 Steiness, L. Acta med. scand. *165* 195 1959

220. Steiness, I Acta med. scand. *170* 319 1961

221 Steiness, L. Acta med. scand *169* 17 1961

222. Steiness, L. Acta med. scand., Suppl. 394 1963

223 Strandness, D E. Jr Priest, R. E. & Gibbons, G E. Diabetes *13* 366, 1964

224. Slive-Søderbergh, J Angervall, L. & Fagerberg, S. E. Diabetologia *3* 331 1967

225 Terkildsen, A. B & Christensen, N J Diabetologia *7* 113, 1971

226. Thomas, P K. & Lascelles, R. G Quart. J Med. *35* 489 1966.

227 Thomsen, J A. Clin. Sci. *26*, 55 1964

228. Trap-Jensen, J Alpert, J S., Rio, G del & Lassen, N A. Acta med. scand. Suppl. 476, 135 1967

229 Trap-Jensen, J & Lassen, N A. Scand. J clin. Lab. Invest. *21* 116 1968

230 Trap-Jensen, J & Lassen, N. A. In Capillary Permeability (ed. Crone, C., & Lassen, N A.). Copenhagen, 1970 (page 135).

231 Trendelenburg, U J Pharmacol. exp. Ther *125* 55 1959

232. Vracko, R. Circulation *51* 271 1970.

233 Wahlberg, F Acta med. scand. *180* suppl 455 1966.

234 Ward, J D Fisher D J Barnes, C. G & Jessop, J D Lancet *I* 428, 1971

235 Weber H. W & Wicht, C. L. S. Afr J Lab. clin. Med. *8* 83, 1962.

236 West, R. O Sawrey K. R., Bird, G S Wilson, D L. & Hatcher J D Clin. Sci. *29* 41 1965

237 Whitby L. G Hertting, G & Axelrod, J Nature *187* 604, 1960.

238 White, P Diabetes *5* 445 1956.

239 Wiswell, J G Hurwitz, G E., Coronho, V Bing, O H L. & Child, D L. J Clin. Endocrin. *23* 1102, 1963

240. Wojcikiewicz, O Blcz, N & Szopinska-Ciba, L. Pol. med. J *5* 810 1966.

241 Woltman, H. W & Wilder R. M Arch. intern. Med. *44* 576, 1929

242. Woolam, G L., Schnur P L., Vallbona, C. & Hoff, H E. Circulation *25* 533 1962.

243 Yu, S. Y In Cowdry's Arteriosclerosis (Ed. Blumenthal, H. T) C. C. Thomas 1967 p. 170.

244 Østerby R. Cited by Lundbæk, K. in Nobel Symposium 13 Pathogenesis of Diabetes mellitus (ed. E. Cerasi, & R. Luft). Uppsala 1970 (page 288).